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Tetrahedron
Tetrahedron 61 (2005) 1221–1244

Synthesis of substituted pyrrolidines and piperidines from endocyclic enamine derivatives. Synthesis of (±)-laburnamine

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Received 3 September 2004; revised 2 November 2004; accepted 15 November 2004

Available online 23 December 2004

Abstract—Functionalization of the α- and β-positions of readily available endocyclic enamine derivatives provides a convenient method for the formation of substituted pyrrolidines and piperidines. α-Alkoxy-β-iodopyrrolidines are formed by the electrophilic addition of iodine to the endocyclic enamine double bond of an *N*-substituted 2-pyrroline, and nucleophillic attack by an alcohol on the intermediate iodonium ion. The resultant α-alkoxy-β-iodopyrrolidines can be used in radical cyclization reactions to give bicyclic hemiaminal compounds, which can be further elaborated using *N*-acyliminium chemistry to form α,β-*cis*-dialkylsubstituted pyrrolidines. A strategy for the incorporation of amino functionality at the β-position was also established by using iodoamination of the enamine double bond, followed by migration of the amine functionality through an aziridination/methanolysis protocol. An alternative method uses an azidomethoxylation protocol using ceric ammonium nitrate (CAN) in the presence of NaN_3 and methanol. Formation and trapping of the *N*-acyliminium ions derived from these substrates, afforded the 3-carbamate and 3-azido-2-substituted products with good diastereoselectivity, with the preferential formation of the *trans* and *cis* stereoisomers, respectively. Using the sequential iodoamination, aziridination in methanol and *N*-acyliminium transformation, *trans*-3-$NHCO_2Me$-2-allyl-pyrrolidine was prepared, which was used as the key precursor in a synthesis of the natural 1-amidopyrrolizidine alkaloid, (±)-laburnamine.

1. Introduction

The importance of substituted pyrrolidines and piperidines as biologically active compounds and their widespread occurrence in alkaloids, have led to the development of numerous synthetic methods for their preparation.[1] An example of these targets are 3-aminopyrrolidine and 3-aminopiperidines, which are useful building blocks for the construction of bioactive compounds.[2] As part of our ongoing interest in the functionalization of *N*-acylated cyclic enamines, we have developed synthetic methodologies for the functionalization of the α and β position of the pyrrolidine or piperidine ring.[3] In this paper, we will present these simple sequential strategies, starting with oxidation processes using electrophilic iodine or ceric ammonium nitrate (CAN). Further manipulation through radical cyclizations, aziridination/methanolysis and/or *N*-acyliminium chemistry provides ready access to a structurally diverse range of pyrrolidines and piperidines, including the 3-aminopyrrolidine and 3-aminopiperidine units.

2. Results and discussion

The electron-rich alkene bond of endocyclic *N*-acylenamides presents numerous synthetic opportunities. Perhaps the most versatile application of such derivatives would be the simultaneous addition of an electrophile (E) and a nucleophile (Nu) to the C=C bond, in what is formally a three-component coupling reaction (Fig. 1). This process results in the simultaneous functionalization of the

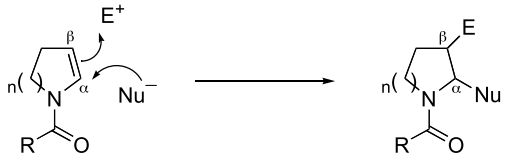

Figure 1. Three component coupling of an endocyclic enamide with an electrophile and a nucleophile.

Keywords: Enamines; Radical cyclizations; Aziridination; *N*-Acyliminium; 1-Amidopyrrolizidine; (±)-Laburnamine.
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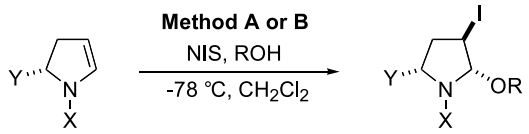
doi:10.1016/j.tet.2004.11.035

Table 1. Examples of iodoetherification of *N*-acyl-enamide precursors



1a: X = Cbz, Y = H
1b: X = acetyl, Y = H
1c: X= Boc, Y = COOMe

2

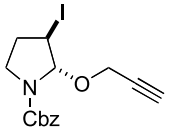
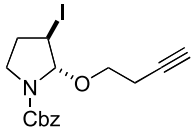
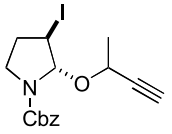
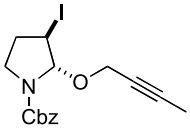
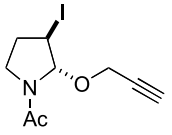
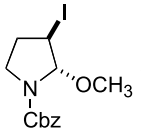
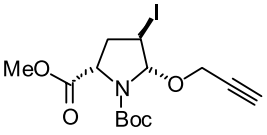
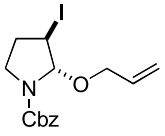
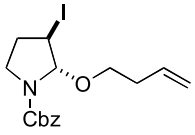
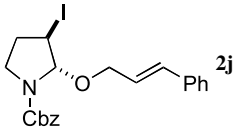
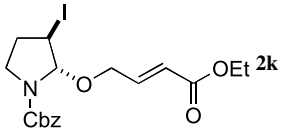
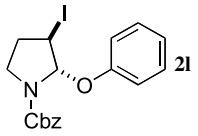
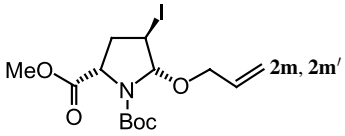
Entry	*N*-Acyl-2-pyrroline	Alcohol	Major product	Method[a]	Yield[b] (%)
1	**1a**	Propargyl alcohol	 **2a**	A	80
2	**1a**	3-Butyn-1-ol	 **2b**	A	75
3	**1a**	3-Butyn-2-ol	 **2c**	A	50[c]
4	**1a**	2-Butyn-1-ol	 **2d**	A	65
5	**1b**	Propargyl alcohol	 **2e**	A	83
6	**1a**	Methanol	 **2f**	A	92
7	**1c**	Propargyl alcohol	 **2g, 2g′**	A	57[c]
8	**1a**	Allyl alcohol	 **2h**	B	65
9	**1a**	3-Buten-1-ol	 **2i**	B	62
10	**1a**	Cinnamyl alcohol	 **2j**	B	74
11	**1a**	Ethyl-(2*E*)-hydroxy-2-butenoate	 **2k**	B	62

Table 1 (*continued*)

Entry	*N*-Acyl-2-pyrroline	Alcohol	Major product	Method[a]	Yield[b] (%)
12	**1a**	Phenol	 **2l**	B	57
13	**1c**	Allyl alcohol	 **2m**, **2m′**	B	88[d]

[a] Method A: **1** was added to a mixture of NIS and ROH in CH_2Cl_2. Method B: NIS was added to a mixture of **1** and ROH in CH_2Cl_2.
[b] Yield of purified product isolated by flash chromatography.
[c] Isolated as a mixture of two diastereomers, ratio not determined.
[d] The two diastereomers were separated by column chromatography, and isolated in a 57:43 ratio.

α- and β-positions of these substrates, with the electrophilic addition step to the more electron-rich β-position triggering the subsequent addition of the nucleophile at the electrophilic α-position.[4] This process would represent an excellent strategy for diversification of the central *N*-heterocyclic scaffold, assuming conditions can be found that prevent the direct competitive attack of the nucleophile with the electrophile. One way, in which this can be accomplished is to use an electrophile–nucleophile combination that are unreactive together. This situation occurs when the electrophile and nucleophile are both heteroatom based, since the direct reaction would result in the formation of a weak E–Nu bond. We have therefore focused upon this approach using heteroatom based electrophiles (e.g. $E^+ = I^+$) to trigger the addition. The addition products can be further elaborated. In this paper, we describe three such processes: (i) free radical cyclizations from the β-position, (ii) substituent rearrangement from the α to β-position, and (iii) nucleophilic attack at the α-position via N-acyliminium chemistry.

The synthetic potential of the *N*-acyl-enamide endocyclic double bond, was first explored by performing electrophilic iodine additions. Treatment of enamide substrates **1a**,[5] **1b**[5] and **1c**[6] with various alcohols in the presence of *N*-iodosuccinimide (NIS) afforded the *trans*-2-alkoxy-3-iodopyrrolidines **2** (Table 1). The high levels of *trans* diastereoselectivity arise because the intermediate iodonium ion undergoes *anti* nucleophilic attack at the α-position.[7] The transformations readily occur at −78 °C, even for less nucleophilic substrates (Table 1, entry 12), and no side reaction was observed between iodine and the unsaturated alcohols, because of the greater nucleophilicity of the enamine π-bond over the alkenol/alkynol π-bonds (Table 1, entries 8–11 and 13). Reaction of the chiral substrate **1c**, which contains an ester group at the 5-position of the pyrroline ring, resulted in poor facial selectivity for the electrophilic addition step, although the products again had a *trans*-relationship between the 3-iodo- and 2-alkoxy substituents (Table 1, entries 7 and 13).

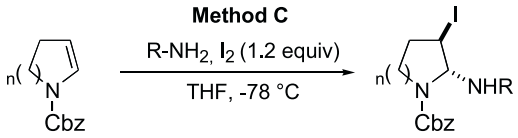
Iodine promoted addition of nitrogen nucleophiles[8,9] on substrates **1a** and **1d** is also possible. Attempts to use primary amines (allylamine and propargylamine), dialkylamines (*N*-methylallylamine and *N*-cyclohexylamine), arylamines (aniline, *N*-acetylaniline) and amides (acrylamide and trifluoracetamide) failed to give stable products.[10] However, the addition of carbamates as the nucleophilic component did give stable addition products, affording a *trans*/*cis* mixture of 3-iodo-2-carbamate substituted pyrrolidines **3a**–**3d** in good yields (Table 2). This transformation occurs at low temperature and uses I_2 instead of *N*-iodosuccinimide, to prevent competitive nucleophilic attack of succinimide on the electrophilic intermediate. Interestingly, in the case of the 6-membered substrate **1d**, only the Boc-carbamate yielded a stable addition product[11] (Table 2, entry 5).

Free-radical cyclization methods, particularly in a 5-*exo* or 6-*exo* manner, constitute one of the most powerful and versatile methods for the construction of cyclic systems and have found extensive application in the synthesis of carbocycles and heterocycles.[12] Radical cyclization reactions of *trans*-α-alkoxy-β-iodopyrrolidines **2** using a sodium cyanoborohydride-catalytic tributylstannane system, generated the bicyclic compounds **4** (Table 3).[7,13] The yields were moderate to high, except for the 6-*exo* ring closures where the direct reduction pathway was strongly competitive (Table 3, entries 2 and 8). The cyclizations were highly regiospecific with only the *cis*-fused 5-*exo* or 6-*exo* products being formed. Such selectivity is well known in radical cyclization reactions. In the 5-*exo* and 6-*exo* cyclization onto alkenes a new asymmetric center is formed (Table 3, entries 7 and 9–12), with the *endo*-isomer being preferentially formed.[14]

However, as the alkene substituent in **2** becomes bulkier, the steric interaction at the *endo* position becomes larger and the selectivity diminishes. For the 6-*exo*-trig ring closure and as expected for acyclic examples,[15] a lower selectivity in favor of the *trans* product was observed (Table 3, entry 8) resulting from the *exo* (1,6-*trans*) transition state.

The above results illustrate the utility of introducing β-I and α-N/O functionality on the C=C bond of endocyclic enamide derivatives. A further goal of our research was to establish whether the endocyclic enamides **1**, or the corresponding 3-iodo-2-carbamate derivatives **3**, could be functionalized to give compounds having β-amino functionality (i.e. 3-aminopyrrolidines/piperidines). Although comparable amino functionalization of glycals (cyclic enol ethers) has been intensively studied in the glycoconjugate

Table 2. Iodocarbamation of *N*-Cbz-enamide substrates



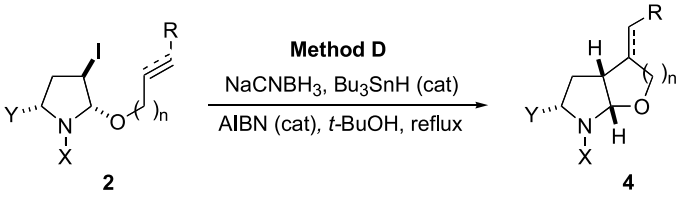
1a: n=1
1d: n=2

3

Entry	Substrate	Product	Yield (%)[a]	d.r.[b]
1	**1a** ($n=1$)	**3a** (R=Boc)	74	72:28
2	**1a** ($n=1$)	**3b** (R=Cbz)	71	77:23
3	**1a** ($n=1$)	**3c** (R=CO_2Me)	70	73:27
4	**1a** ($n=1$)	**3d**[c] (R=Ts)	32[c]	69:31
5	**1d** ($n=2$)	**3e** (R=Boc)	75	—

[a] Yield of pure product purified by flash chromatography.
[b] Determined by ^{1}H NMR.
[c] Partial decomposition was observed within a few days at 4 °C.

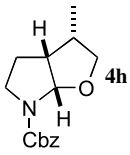
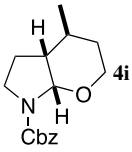
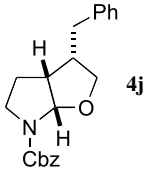
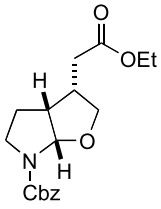
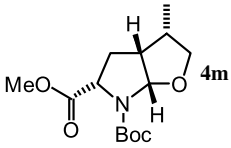
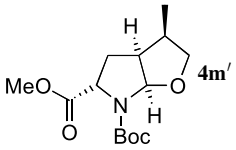
Table 3. Conversion of pyrrolidines **2** into bicyclic pyrrolidines **4**



2 **4**

Entry	Pyrrolidine	Bicyclic	Yield (%)[a]	*endo*/*exo*
1	**2a**	**4a**	71	—
2	**2b**	**4b**	46[b]	—
3	**2c**	**4c**	61	—
4	**2d**	**4d**	74[c]	—
5	**2e**	**4e**	75	—
6	**2g**	**4g**, **4g′**	61	—

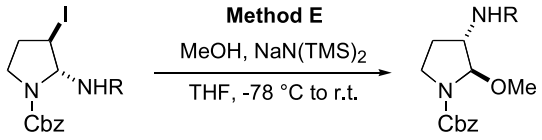
Table 3 (*continued*)

Entry	Pyrrolidine	Bicyclic	Yield (%)[a]	*endo*/*exo*
7	**2h**	 **4h**	92[d]	95:5
8	**2i**	 **4i**	30[d,e]	40:60
9	**2j**	 **4j**	66[d]	74:26
10	**2k**	 **4k**	82[d]	80:20
11	**2m**	 **4m**	96[d]	95:5
12	**2m′**	 **4m′**	76[d]	95:5

[a] Yield of purified product isolated by flash chromatography.
[b] The corresponding uncyclized reduced product was isolated in 37% yield.
[c] Isolated as a 1:1 mixture of *E*/*Z* isomers.
[d] The stereochemistry of the products were assigned by a combination of 1D NMR and 2D NMR NOESY experiments performed at 360 K in 1,1,2,2-d_2-tetrachloroethane.
[e] The corresponding uncyclized reduced products were also isolated in 26% yield.

chemistry, very few examples are known for N-heterocyclic equivalents.[16] The most straightforward pathway would involve a direct aminohydroxylation protocol on the endocyclic substrates **1**, but initial attempts to achieve such reactions have failed.[17] However, *cis*/*trans*-2-methoxy-3-*N*-(trifluoroacetyl)aminopyrrolidines have been prepared,[17] albeit in moderate yields, via a formal aziridination protocol using a manganese nitrido complex.[18]

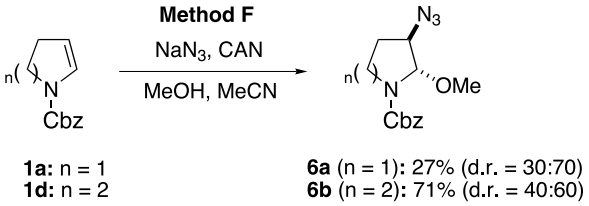
Table 4. Aziridination/methanolysis of **3**



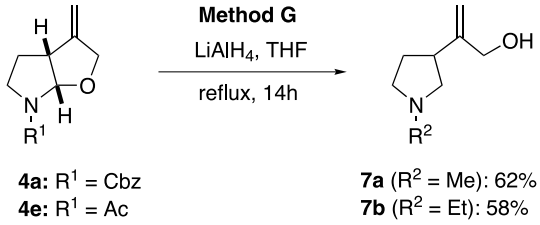
3 **5**

Entry	Substrate	Product	Yield (%)[a]	d.r.[b] (*trans*/*cis*)
1	**3a**	**5a** (R=Boc)	82	85:15
2	**3b**	**5b** (R=Cbz)	73	77:23
3	**3c**	**5c** (R=MeOCO)	85	78:22

[a] Yield of purified pure product isolated by flash chromatography.
[b] Determined by ^{1}H NMR.



Scheme 1. Azidomethoxylation with ceric ammonium nitrate (CAN).



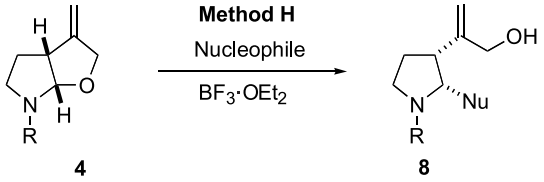
Scheme 2. $LiAlH_4$ Reduction of bicyclic hemiaminal derivatives **4**.

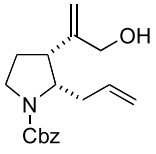
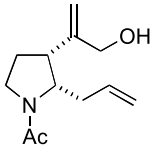
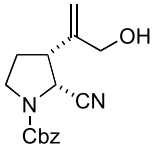
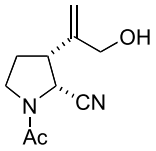
The adducts described above provide an alternative approach for the introduction of β-amino functionality. A migration/methanolysis protocol on **3** allows for the preparation of 3-amino-2-methoxy functionalized pyrrolidines and piperidines. Treatment of compounds **3a**–**3c** with $NaN(SiMe_3)_2$ in THF and methanol, results in cyclization to give an aziridine intermediate, which is then ring-opened in situ at low temperature by methanol, to afford inseparable diastereomeric mixtures of **5a**–**5c** (Table 4). The same transformation could also be achieved, but in lower yields (60% for **5a** and 59% for **5b**), using KOH (0.1 M)/MeOH at 35 °C for 5 h.[19]

Surprisingly the aziridination/methanolysis protocol was unsuccessful on the piperidine substrate **3e**. However, treatment of the enecarbamates **1a** or **1d** with CAN[20,21] in the presence of sodium azide and methanol afforded 3-azido-2-methoxypyrrolidines **6a** and piperidine **6b** respectively, as diastereomeric mixtures (Scheme 1). This azidomethoxylation protocol allows for the introduction of latent amino functionality, as an azido group, in the β position of both pyrrolidines and piperidines. Interestingly, this reaction occurred in much better yields using the piperidine substrate **1d** than with the pyrrolidine substrate **1a**.

Both the bicyclic compounds **4** and the 2-methoxy-3-substituted-pyrrolidines **2**, **5** and **6** constitute versatile intermediates by virtue of the hemiaminal functionality, which can undergo reaction with nucleophiles at the α-position. The simplest nucleophilic addition reaction is hydride addition, as exemplified by the use of lithium aluminium hydride.[22] For example, substrates **4a** and **4e**

Table 5. *N*-Acyliminium ion additions of bicyclic hemiaminal derivatives **4**



Entry	Substrate	Nucleophile	Major product[a]	Yield (%)[b]	d.r.[c] (*cis*/*trans*)
1	**4a** (R=Cbz)	$H_2C{=}CHCH_2SiMe_3$	 **8a**	89	76:24
2	**4e** (R=Ac)	$H_2C{=}CHCH_2SiMe_3$	 **8b**	58	63:37
3	**4a** (R=Cbz)	Me_3SiCN	 **8c**	76	67:33
4	**4e** (R=Ac)	Me_3SiCN	 **8d**	64	74:26

[a] The stereochemistry of the products were assigned by a combination of 1D and 2D NMR NOESY experiments performed at 360 K in 1,1,2,2-tetrachloroethane-d_2.
[b] Yield of purified pure product isolated by flash chromatography.
[c] Determined by ^1H NMR.

underwent reduction to *N*-alkyl-3-alkyl-substituted pyrrolidines in moderate yields (Scheme 2).

More importantly these compounds can be utilized as *N*-acyliminium ion precursors in C–C bond forming reactions[23] as exemplified by reactions with allyltrimethylsilane or cyanotrimethylsilane. Reaction of **4** with these nucleophiles in the presence of $BF_3 \cdot OEt_2$ gave compounds **8a**–**8d** in moderate diastereoselectivity. The major diastereomers were the *cis*-isomers,[24] as determined by 2D-NOESY experiments (Table 5) and, in the case of compound **8d**, further confirmed by an X-ray structure determination (Fig. 2).

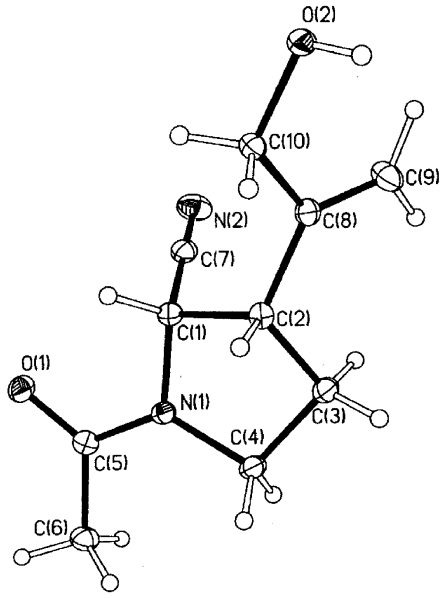


Figure 2. Representation of the X-ray structure of **8d**.

Further transformations of *N*-acyl-iminium intermediates derived from 3-carbamate and 3-azido substituted pyrrolidines **5** and piperidines **6** would be of special interest because they would allow for the preparation of potential precursors for natural and non-natural products synthesis.[25] Reaction of allyltrimethylsilane, cyanotrimethylsilane or *tert*-butyl[1-ethoxyvinyl)oxy]dimethylsilane with pyrrolidines **5a**–**5c** under Lewis acidic conditions afforded the 3-carbamate-2-alkyl-substituted pyrrolidines **9a**–**9d** in moderate to good yields, and with moderate *trans* stereoselectivity (Table 6, entries 1–4). This observed *trans* selectivity can be rationalized by a neighboring group effect.[26] In contrast, similar attack of the 3-azido substrates **6a** and **6b** gave substituted products **9e** and **9f** with moderate yields and high *cis* selectivity[24] (Table 6, entries 5 and 6). Analogous *N*-acyliminium transformations could also be performed on 3-iodo-2-methoxypyrrolidine **2f** to give the substituted products **9g** and **9h** in good to excellent yields (Table 6, entries 7 and 8). These products were obtained exclusively as the *trans* diastereomers, presumably via the intermediacy of an iodonium ion, which exclusively directs the nucleophilic attack in an *anti* fashion.

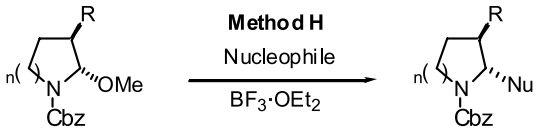
Pyrrolizidines are an important class of alkaloids, present in many plants and insects. They are important synthetic targets due to their toxicological and biological properties,[27] and indeed, synthesis of pyrrolizidines have been a fertile testing ground for new synthetic methodologies.[28] 1-Aminopyrrolizidines are a relatively rare subclass, and only a few representatives have been described.[29] There has been some synthetic effort to construct related structures.[30] Recently Potier and co-workers[31] described the first synthesis of two 1-amidopyrrolizidine alkaloids, absouline and laburnamine, through a pyrrolizidine-1-one hydrochloride intermediate.

The availability of 3-aminopyrrolidines through the methodology outlined in this paper, provides an alternative strategy for the formation of the 1-aminopyrrolizidine skeleton (Scheme 3). Thus, the major *trans*-isomer of **9d** was readily separated from the *cis*-isomer by flash column chromatography. Hydroboration of compound *trans*-**9d** using $BH_3 \cdot SMe_2$[32] followed by oxidative hydrolysis with $NaOH/H_2O_2$ afforded the alcohol **10**. Initial attempts using $BH_3 \cdot THF$[33] or 9-BBN[33] required long reaction times and, in the latter case, resulted in difficulties in purification. In an attempt to form a reductive amination precursor, oxidation of the primary alcohol **10** to the aldehyde was attempted using NMO/TPAP,[34] but this intermediate proved to be unstable. Alternatively tosylation[35] of the primary alcohol afforded compound **11** which upon hydrogenation[36] (5% Pd/C) cyclized to give 1-carbamate pyrrolizidine **12**. Carbamate deprotection was accomplished with TMSI followed by methanolysis[37] and the crude amine was immediately protected with methylbutyric acyl chloride to give (±)-laburnamine **13** in an overall yield of 6% starting from the enecarbamate **1a**.

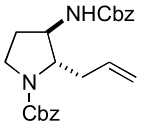
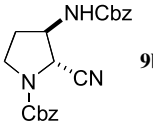
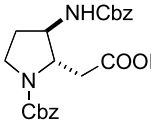
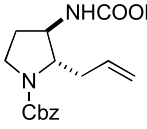
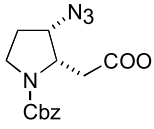
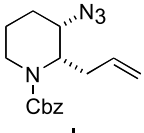
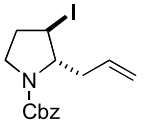
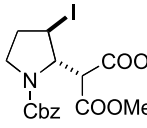
3. Conclusions

In summary, strategies for pyrrolidine and piperidine α,β-funcionalization have been developed, starting from readily available endocyclic enamine derivatives. A two step heteroannulation procedure involving iodoetherification of *N*-acyl-2-pyrrolines followed by radical cyclization, gave access to the bicyclic compounds **4** which can be used in further transformations to form substituted pyrrolidines. 3-Amino functionalization of pyrrolidines and piperidines can be accomplished by two different routes, from the corresponding endocyclic enamine derivatives. Iodoamination followed by aziridination/methanolysis afforded the 3-carbamate-2-methoxypyrrolidines **5** and azidomethoxylation with CAN/NaN_3 in methanol afforded the 3-azido-2-methoxypyrrolidines **6a** and piperidines **6b**. Stereoselective substitution of the 2-methoxy group by carbon nucleophiles via *N*-acyliminium intermediates afforded the 2-substituted-3-carbamate-pyrrolidines (**9a**–**9d**) with good *trans*-selectivity and the 2-substituted-3-azido-pyrrolidines and piperidines with good *cis*-selectivity (**9e** and **9f**). The resultant compounds are useful synthetic intermediates, as exemplified by the synthesis of the natural 1-aminopyrrolizidine alkaloid, (±)-laburnamine, starting from the pyrrolidine precursor **9d**. Overall, this study further establishes the utility of electron-rich endocyclic enecarbamates (or enamides) in electrophilic addition reactions.

Table 6. *N*-Acyliminium ion additions of 2-methoxy-3-substituted pyrrolidine precursors



9

Entry	Substrate	Nucleophile	Major product[a]	Yield (%)[b]	d.r.[c] *cis*/*trans*
1	**5b** ($n=1$, R=NHCbz)	$H_2C{=}CHCH_2SiMe_3$	 **9a**	60	24:76
2	**5b** ($n=1$, R=NHCbz)	Me_3SiCN	 **9b**	52	30:70
3	**5b** ($n=1$, R=NHCbz)	$CH_2{=}C(OTBDMS)OEt$	 **9c**	74	15:85
4	**5c** ($n=1$, R=$NHCO_2Me$)	$H_2C{=}CHCH_2SiMe_3$	 **9d**	79	23:77
5	**6a** ($n=1$, R=N_3)	$CH_2{=}C(OTBDMS)OEt$	 **9e**	49	88:12
6	**6b** ($n=2$, R=N_3)	$H_2C{=}CHCH_2SiMe_3$	 **9f**	50	88:12
7	**2f** ($n=1$, R=I)	$H_2C{=}CHCH_2SiMe_3$	 **9g**	93	≤2:98
8	**2f** ($n=1$, R=I)	$CH_2(CO_2Me)_2$	 **9h**	68[d]	≤2:98

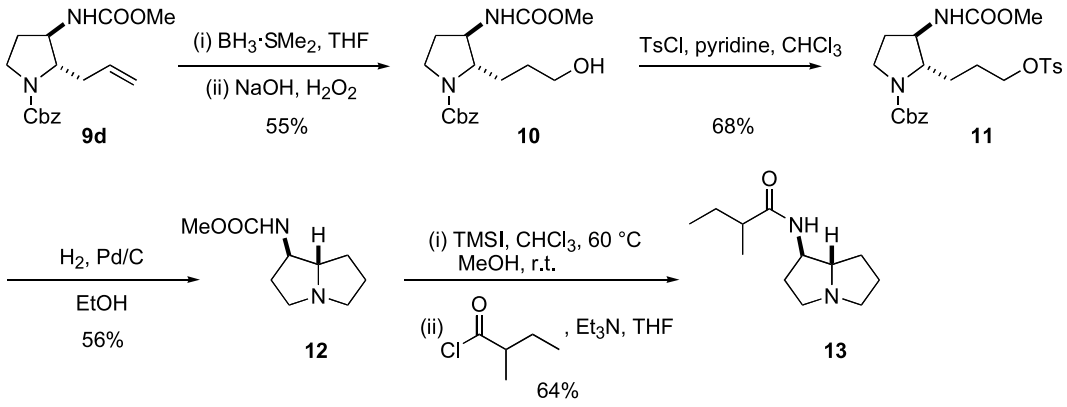
[a] The stereochemistry of the products were assigned by a combination of 1D and 2D NMR NOESY experiments performed at 360 K in 1,1,2,2-tetrachloroethane-d_2.
[b] Yield of purified pure product isolated by flash chromatography.
[c] Determined by ^{1}H NMR.
[d] Prepared at −78 °C and using $TiCl_4$ as the Lewis acid.

4. Experimental

4.1. General remarks

All chemicals were purchased from commercial sources and were used without further purification. Unless otherwise stated, all reactions were performed under nitrogen or argon atmosphere using flame or oven (120 °C) dried glassware. Diethyl ether, tetrahydrofuran (THF), benzene and toluene were distilled over sodium and benzophenone under argon or nitrogen. Dichloromethane, *t*-BuOH and acetonitrile were distilled over CaH_2. Analytical thin-layer chromatography (TLC) was performed on silica gel plates (Merck Kiesegel GF 254, 0.2 mm) and components were visualized by observation under UV light or by treating the plates with phosphomolybdic reagent followed by heating. Column chromatography was carried out using Merck 60H silica gel or Whatman 230–400 'mesh' silica gel. Solvent ratios for R_f values are reported as v/v.

Nuclear magnetic resonance spectra: ^{1}H and ^{13}C NMR spectra were recorded on either Varian Gemini 200, Bruker ARX 400 or Varian XL400 MHz spectrometers. The following abbreviations are used to indicate signal



Scheme 3. Synthesis of (±)-laburnamine.

multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; br, broad and *J*, coupling constant in Hz. Infrared spectra were recorded on either a Buck Scientific M-500 or a Fourier Perkin–Elmer 683 spectrometer. Melting points were measured on a Köpfler instrument, mod. Reichert Termovar and are uncorrected. Optical activities were measured on an Optical activity, Mod. AA-1000, with a 5 cm cell. Low-resolution mass spectra were performed on Bell and Howell 21-490 spectrometer and high resolution mass spectra were performed on a AEI MS3074 spectrometer (University of Toronto). X-ray crystallography analysis was performed by Dr. Alan Lough (Department of Chemistry, University of Toronto).

CCDC-249610 **8d** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk).

4.2. Method A. General procedure for iodoetherification with alkynols

To a solution of *N*-iodosuccinimide (1.2 mequiv) and the alcohol (1.2 mequiv) in dry dichloromethane at −78 °C, was added dropwise *N*-acyl-2-pyrroline **1** (1.0 mequiv). The mixture was stirred under argon for 10 min and then poured into a cold saturated aqueous solution of $NaHCO_3$. The aqueous phase was extracted twice with dichloromethane. The combined organic phases were dried (Na_2SO_4) and the solvent removed in vacuo to yield the iodoether **2** derivative, which was purified by flash chromatography.

4.2.1. *trans*-Benzyl-3-iodo-2-(2-propynyloxy)-1-pyrrolidine carboxylate (2a, Table 1, entry 1). Prepared following method A using propargyl alcohol (172 µl, 2.95 mmol), *N*-iodosuccinimide (698 mg, 2.95 mmol) and *N*-[(benzyloxy)carbonyl)]-2-pyrroline (**1a**) (500 mg, 2.46 mmol), to yield the iodoether derivative which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording **2a** (760 mg, 80%) as a colorless oil; R_f=0.5 (10% EtOAc/90% hexane); IR (film) ν 3290, 3032, 2955, 2117, 1710, 1586, 1498, 1404, 1286, 1193, 1113, 1052, 972, 915, 772, 697 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), rotamers, δ 7.36–7.33 (m, 5H, Ar), 5.63–5.54 (m, 1H, N–C*H*–O), 5.19 (s, 2H, –CH_2Ph), 4.33–4.31 (m, 2H, –OCH_2C≡C), 4.12 (d, J=3.6 Hz, 1H, –C*H*I), 3.71–3.49 (m, 2H, –NCH_2CH_2), 2.48–2.11 (m, 3H, –C≡C*H* and –NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 156.4, 154.2, 136.7, 127.5, 128.5, 129.1, 95.4, 94.3, 80.2, 79.8, 75.2, 67.7, 56.6, 55.5, 45.2, 33.1, 32.5, 26.5, 26.0; HRMS (EI) *m/z* calcd for ($C_{15}H_{16}INO_3^+$): 385.0175, found: 385.0173.

4.2.2. *trans*-Benzyl-2-(3-butynyloxy)-3-iodo-1-pyrrolidine carboxylate (2b, Table 1, entry 2). Prepared following method A using 3-butyn-1-ol (295 µl, 3.03 mmol), *N*-iodosuccinimide (716 mg, 3.03 mmol) and **1a** (513 mg, 2.53 mmol) to yield the iodoether derivative which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording **2b** (760 mg, 75%) as a colorless oil; R_f=0.42 (20% EtOAc/80% hexane); IR (film) ν 3294, 3032, 2953, 1712, 1497, 1407, 1192, 1112, 916, 771, 697, 604 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), rotamers, 7.35 (br, 5*H*, Ar), 5.42–5.54 (m, 1H, NC*H*–O), 5.22–5.18 (m, 2H, –CH_2Ph), 4.25 (d, J=4.8 Hz, 1H, –C*H*I), 3.76–3.53 (m, 4H, –NCH_2 and –OCH_2) 2.45–1.98 (m, 5H, –C≡C*H*, –NCH_2CH_2 and –CH_2C≡CH); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 156.2, 155.3, 136.3, 128.4, 128.3, 128.0, 127.9, 96.2, 96.1, 81.7, 81.5, 69.5, 69.4, 67.3, 67.1, 66.7, 66.4, 33.6, 32.7, 26.9, 26.3, 19.9, 19.8; HRMS (EI) *m/z* calcd for ($C_{16}H_{18}INO_3^+$): 399.0331, found: 399.0316.

4.2.3. *trans*-Benzyl-3-iodo-2-[(1-methyl-2-propynyl)oxy]-1-pyrrolidinecarboxylate (2c, Table 1, entry 3). Prepared following method A using 3-butyn-2-ol (238 µl, 2.95 mmol), *N*-iodosuccinimide (698 mg, 2.95 mmol) and **1a** (500 mg, 2.46 mmol) to yield the iodoether derivative which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording **2c** (487 mg, 50%) as a colorless oil; R_f=0.22 (10% EtOAc/90% hexane); IR (film) ν 3294, 2983, 2895, 1706, 1558, 1539, 1505, 1456, 1405, 1358, 1338, 1282, 1259, 1212, 1186, 1113, 1045, 1008, 912, 734, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.35–7.24 (m, 5H, Ar), 5.67 (s, 0.5H, NC*H*O), 5.53 (s, 0.5H, NC*H*O), 5.27–5.07 (m, 2H, –CH_2Ph), 4.57 (q, J=6.6 Hz, 0.5H, –C*H*CH$_3$), 4.38 (t, J=6.8 Hz, 1H, –C*H*I), 4.22 (q, J=6.7 Hz, 0.5H, –C*H*CH$_3$), 3.70–3.52 (m, 2H, –NCH_2), 2.56–2.39 (m, 2H, –NCH_2CH_2 and –C≡C*H*), 2.14–2.08 (m, 1H, –NCH_2CH_2), 1.38 (d, J=6.6 Hz, 1.5H, –CHCH_3), 1.24 (d,

J=6.8 Hz, 1.5H, –CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.4, 154.5, 136.2, 136.1, 128.4, 128.1, 128.1, 128.0, 127.7, 94.8, 94.3, 83.9, 94.3, 83.9, 83.7, 73.1, 67.4, 67.2, 64.5, 63.8, 44.8, 44.7, 33.6, 32.7, 27.8, 27.0, 22.1, 21.9; HRMS (EI) m/z calcd for ($C_{16}H_{18}INO_3^+$): 399.0331, found: 399.0316.

4.2.4. *trans*-Benzyl-2-(2-butynyloxy)-3-iodo-1-pyrrolidinecarboxylate (2d, Table 1, entry 4). Prepared following method A using 2-butyn-1-ol (115 µl, 1.54 mmol), *N*-iodosuccinimide (362 mg, 1.54 mmol) and **1a** (260 mg, 1.28 mmol) to yield the iodoether derivative which was purified by flash column chromatography (SiO_2, 5% EtOAc/95% hexane) affording **2d** (334 mg, 65%) as a colorless oil; R_f=0.68 (10% EtOAc/90% hexane); IR (film) ν 3032, 2954, 1712, 1498, 1407, 1359, 1285, 1192, 1113, 1043, 975, 912, 771, 698, 603 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$), rotamers, δ 7.35–7.24 (m, 5*H*, Ar), 5.9–5.7 (m, 0.4H, –NC*H*–O), 5.6 (s, 0.3H, –NC*H*–O), 5.5 (s, 0.3H, –NC*H*–O), 5.26–5.1 (m, 2H, –CH_2Ph), 4.56–4.20 (m, 2H, –OCH_2-C≡CH), 4.08–4.07 (m, 1H, –C*H*I), 3.72–3.5 (m, 2H, –NCH_2), 2.62–2.46 (m, 1H, –NCH$_2$CH_2), 2.14–2.04 (m, 1H, –NCH$_2$CH_2), 1.84 (s, 1.5H, –C≡CCH_3), 1.77(s, 1.5H, –C≡CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.9, 155.5, 136.1, 136.0, 128.5, 128.4, 128.3, 128.1, 127.8, 95.0, 94.2, 89.8, 89.2, 82.8, 82.7, 74.9, 74.6, 67.4, 67.2, 57.2, 56.5, 45.1, 44.7, 33.6, 33.0, 26.5, 26.3, 3.6, 3.5; HRMS (EI) m/z calcd for ($C_{16}H_{18}INO_3^+$): 399.0331, found: 399.0326.

4.2.5. *trans*-1-Acetyl-3-iodo-2-(2-propynyloxy)pyrrolidine (2e, Table 1, entry 5). Prepared following method A using propargyl alcohol (377 µl, 6.48 mmol), *N*-iodosuccinimide (1.53 g, 6.48 mmol) and *N*-[(methyl)carbonyl]-2-pyrroline **1b** (0.60 g, 5.4 mmol) to yield the iodoether derivative which was purified by flash column chromatography (SiO_2, 30% EtOAc/70% hexane) affording **2e** (1.31 g, 83%) as a colorless oil; R_f=0.28 (30% EtOAc/70% hexane); IR (film) ν 3290, 2950, 1667, 1651, 1404, 1360, 1263, 1181, 1143, 1055, 921, 845 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$), rotamers, δ 5.41 (s, 0.5H, –NC*H*O), 5.16 (s, 0.5H, –NC*H*O), 4.24 (d, J=4.8 Hz, 0.5H, –C*H*I), 4.06–3.97 (m, 2.5H, –C*H*I and –OCH_2), 3.34–3.28 (m, 2H, N–CH_2), 2.51–2.50 (m, 0.4H, C≡C*H*), 2.36–2.14 (m, 2.6H, C≡C*H* and –NCH$_2$CH_2), 1.89 (s, 1.5H, CH_3), 1.84 (s, 1.5H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 170.5, 169.6, 93.9, 92.3, 79.3, 77.9, 75.8, 74.2, 56.3, 54.4, 45.0, 43.5, 33.2, 31.3, 26.0, 25.7, 21.8, 21.4; HRMS (EI) m/z calcd for ($C_9H_{12}INO_2+H^+$): 293.9991, found: 293.9976.

4.2.6. *trans*-Benzyl 3-iodo-2-methoxy-1-pyrrolidinecarboxylate (2f, Table 1, entry 6). Prepared following method A using *N*-iodosuccinimide (893 mg, 3.78 mmol), methanol (2 ml) and **1a** (630 mg, 3.15 mmol) to yield the iodoether derivative which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording **2f** (1.05 g, 92%) as a colorless oil; R_f=0.48 (20% EtOAc/80% hexane); IR (film) ν 3016, 2950, 2891, 2822, 1709, 1500, 1445, 1406, 1362, 1337, 1283, 1175, 1111, 1072, 954, 915, 773, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.31–7.19 (m, 5H, Ar), 5.38 (s, 0.6H, –NC*H*O), 5.27 (s, 0.4H, –NC*H*O), 5.18–5.06 (m, 2H, –CH_2Ph), 4.15 (d, J=4.6 Hz, 1H, –C*H*I), 3.66–3.59 (m, 1H, –NCH_2), 3.46 (t, J=8.8 Hz, 1H, –NCH_2), 3.36 (s, 1.5H, CH_3), 3.22 (s, 1.5H, CH_3), 2.48–2.41 (m, 1H, –NCH$_2$CH_2), 2.08–2.03 (m, 1H, –NCH$_2$CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.7, 155.9, 136.4, 128.5, 128.1, 127.8, 127.7, 96.7, 96.2, 67.4, 67.2, 66.7, 56.4, 56.0, 44.9, 44.7, 33.8, 32.9, 29.7, 26.5, 25.8; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.5(+), 128.1(+), 127.8(+), 127.7(+), 96.7(+), 96.2(+), 67.4(−), 67.2(−), 66.7(−), 56.4(+), 56.0(+), 44.9(−), 44.7(−), 33.8(−), 32.9(−), 29.7(−), 26.5(+), 25.8(+); HRMS (EI) m/z calcd for ($C_{13}H_{16}INO_3^+$): 361.0165, found: 361.0175.

4.2.7. 1-*tert*-Butyl-2-methyl-(2*S*(*R*),4*R*(*S*),5*S*)-4-iodo-5-(2-propynyloxy)-1,2-pyrrolidinecarboxylate (2g and 2g′, Table 1, entry 7). Prepared following method A using propargyl alcohol (78 µl, 1.35 mmol), *N*-iodosuccinimide (308 mg, 1.35 mmol) and **1c** (252 mg, 1.12 mmol) to yield the iodoether derivative which was purified by flash chromatography (SiO_2, 20% EtOAc/80% hexane) affording **2g** and **2g′** (260 mg, 57%) as a colorless oil; R_f=0.27 (10% EtOAc/90% hexane); $[\alpha]_D^{20}$=−25.0 ($CHCl_3$, c=0.105 g/100 ml); IR (film) ν 3269, 2977, 2952, 1760, 1713, 1478, 1439, 1378, 1320, 1258, 1203, 1165, 1054, 980, 903, 860, 804, 773, 749, 665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), rotamers, δ 5.59–5.54 (m, 0.8H, –NC*H*O), 5.38 (s, 0.2H, –NC*H*O), 4.61–4.19 (m, 4H, –OCH_2, NC*H*CO$_2$CH$_3$ and –C*H*I), 3.70–3.68 (m, 3H, CO$_2$CH_3), 3.08–2.93 (m, 0.5H, –C≡C*H*), 2.63–2.54 (m, 0.5H, –C≡C*H*), 2.52–2.54 (m, 2H, –NCHCH_2), 1.45 (s, 4.5H, –C(CH_3)$_3$), 1.38 (s, 4.5H, –C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 171.9, 171.8, 171.6, 171.3, 154.0, 153.3, 153.2, 96.5, 94.3, 93.9, 81.5, 81.2, 75.2, 74.8, 74.4, 74.3, 58.8, 58.5, 58.1, 57.6, 56.9, 55.5, 54.4, 52.3, 52.1, 38.6, 38.4, 37.7, 37.1, 28.3, 28.1, 25.2, 24.3, 22.1, 20.7; DEPT (100 MHz, $CDCl_3$), rotamers, δ 96.5(+), 94.3(+), 93.9(+), 81.5(+), 81.2(+), 75.2 (+), 74.8(+), 74.4(+), 74.3(+), 58.8(+), 58.5(+), 58.1(+), 57.6(−), 56.9(−), 55.5(−), 54.4(−), 52.4(+), 52.3(+), 52.1(+), 38.6(−), 38.4(−), 37.7(−), 37.1(−), 28.3(+), 28.1(+), 25.2(+), 24.3(+), 22.1(+), 20.7(+).

4.3. Method B. General procedure for iodoetherification with alkenols

To a solution *N*-acyl-2-pyrroline **1** (1.0 mequiv) and the alcohol (1.2 mequiv) in dry dichloromethane under argon at −78 °C was added via cannula a solution of *N*-iodosuccinimide (1.0 mequiv) in dry dichloromethane (50 ml) and cooled to −78 °C. The resulting mixture was stirred for 10 min and then poured into a cold saturated aqueous solution of $NaHCO_3$. The aqueous phase was extracted once with dichloromethane (40 ml). The combined organic phases were dried (Na_2SO_4) and the solvent removed in vacuo to yield the iodoether derivative **2**, which was purified by flash column chromatography.

4.3.1. *trans*-Benzyl-2-(allyloxy)-3-iodo-1-pyrrolidinecarboxylate (2h, Table 1, entry 8). Prepared following method B using **1a** (1.5 g, 7.4 mmol), allyl alcohol (610 µl, 8.9 mmol) and *N*-iodosuccinimide (1.74 g, 7.39 mmol) to yield the iodoether derivative which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording **2h** (2.1 g, 74%) as a colorless oil; R_f=0.47 (10% EtOAc/90% hexane); IR (film) ν 3031, 2953, 2896, 1713,

1683, 1652, 1506, 1457, 1398, 1360, 1338, 1286, 1193, 1115, 1056, 917, 878, 771, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.36–7.24 (m, 5H, Ar), 5.92–5.84 (m, 0.5H, C*H*=CH_2), 5.82–5.70 (m, 0.5H, C*H*=CH_2), 5.54 (s, 0.5H, –NC*H*O), 5.42 (s, 0.5H, –NC*H*O), 5.30–5.07 (m, 4H, –CH_2Ph and –CH=CH_2), 4.23 (d, J=4.8 Hz, 2H, OCH_2), 3.94 (tt, J=6.8, 1.2 Hz, 1H, –C*H*I), 4.10 (tt, J=6.5, 1.2 Hz, 1H, –C*H*I), 3.74–3.65 (m, 1H, –NCH_2), 3.56–3.50 (m, 1H, –NCH_2), 2.61–2.50 (m, 1H, –NCH_2CH_2), 2.12 (ddd, J= 14.8, 6.8, 2.8 Hz, 1H, –NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.5, 154.6, 136.2, 136.1, 134.2, 133.8, 128.4, 128.1, 128.0, 127.9, 127.6, 117.4, 117.3, 95.1, 94.5, 69.9, 69.4, 67.3, 67.1, 44.8, 44.64, 33.68, 32.7, 27.0, 26.3; HRMS (EI) m/z calcd for ($C_{15}H_{18}INO_3^+$): 387.0331, found: 387.0323.

4.3.2. *trans*-Benzyl-2-(3-butenyloxy)-3-iodo-1-pyrrolidinecarboxylate (2i, Table 1, entry 9). Prepared following method B using **1a** (340 mg, 1.68 mmol), 3-buten-1-ol (177 µl, 2.02 mmol) and *N*-iodosuccinimide (397 mg, 1.68 mmol) to yield the iodoether derivative which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording **2i** (414 mg, 62%) as a colorless oil; R_f=0.38 (10% EtOAc/90% hexane); IR (film) ν 3067, 2951, 2895, 1711, 1640, 1105, 1360, 1335, 1283, 1210, 1192, 1112, 1062, 915, 876, 771, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.34–7.26 (m, 5H, Ar), 5.81–5.62 (m, 1H, C*H*=CH_2), 5.50 (s, 0.5H, –NC*H*O), 5.38 (s, 0.5H, –NC*H*O), 5.24–4.96 (m, 4H, –CH_2Ph and –CH=CH_2), 4.18 (d, J=3.6 Hz, 1H, –C*H*I), 3.72–3.40 (m, 4H, –OCH_2 and –NCH_2), 2.55–2.43 (m, 1H, –NCH_2CH_2), 2.28 (dq, J=6.8, 1.2 Hz, 1H, CH_2CH=CH_2), 2.18 (dq, J=6.8, 1.2 Hz, 2H, –CH_2CH=CH_2), 2.07 (dd, J=14.0, 6.4 Hz, 1H, –NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.2, 154.3, 136.1, 136.0, 134.6, 134.3, 128.2, 127.8, 127.7, 127.6, 127.4, 116.3, 95.1, 94.6, 67.8, 67.5, 67.0, 66.8, 44.6, 44.4, 33.9, 33.7, 33.5, 32.5, 26.9, 26.3; HRMS (EI) m/z calcd for ($C_{16}H_{20}INO_3^+$): 401.0488, found: 401.0494.

4.3.3. *trans*-Benyzl-3-iodo-2-([(2*E*)-3-phenyl-2-propenyl]oxy(-1-pyrrolidinecarboxylate (2j, Table 1, entry 10). Prepared following method B using **1a** (305 mg, 1.50 mmol), cinnamyl alcohol (241 mg, 1.8 mmol) and *N*-iodosuccinimide (353 mg, 1.5 mmol) to yield the iodoether derivative which was purified by flash chromatography (SiO_2, 10% EtOAc/90% hexane) affording **2j** (514 mg, 74%) as a yellow oil; R_f=0.24 (20% EtOAc/80% hexane); IR (film) ν 3028, 2951, 2895, 1712, 1496, 1448, 1403, 1356, 1328, 1267, 1210, 1177, 1112, 1070, 1050, 967, 913, 878, 735, 593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.41–7.24 (m, 10H, Ar), 6.64 (d, J=16.0 Hz, 0.5H, CH=C*H*Ph), 6.46 (d, J=16.0 Hz, 0.5H, –CH=C*H*Ph), 6.33–6.26 (m, 0.5H, –C*H*=CHPh), 6.19–6.12 (m, 0.5H, –C*H*=CHPh), 5.66 (s, 0.5H, –NC*H*O), 5.54 (s, 0.5H, –NC*H*O), 5.32–5.16 (m, 2H, –CH_2Ph), 4.41–4.31 (m, 1H, –OCH_2), 4.29 (d, J=5.2 Hz, 1H, –C*H*I), 4.18–4.11 (m, 1H, –OCH_2), 3.80–3.63 (m, 1H, –NCH_2), 3.61–3.55 (m, 1H, –NCH_2), 2.66–2.53 (m, 1H, –NCH_2CH_2), 2.12 (dd, J= 14.4, 6.4 Hz, 1H, –NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.4, 154.5, 136.4, 136.1, 136.0, 128.3, 127.9, 127.9, 127.8, 127.6, 127.5, 126.3, 126.3, 125.3, 124.8, 95.0, 94.3, 69.5, 68.9, 67.2, 67.0, 44.7, 44.5, 33.6, 32.6, 26.9, 26.3; HRMS (EI) m/z calcd for ($C_{12}H_{13}INO_3^+$, corresponds to β-iodopyrrolidine unit): 329.9991, found: 329.9994.

4.3.4. *trans*-Benzyl-2-([(2*E*)-4-ethoxy-4-oxo-2-butenyl]-oxy(-3-iodo-1-pyrrolidinecarboxylate (2k, Table 1, entry 11). Prepared following method B using **1a** (406 mg, 2.0 mmol), ethyl-(2*E*)-hydroxy-2-butenoate (312 mg, 2.4 mmol) and *N*-iodosuccinimide (460 mg, 2.0 mmol) to yield the iodoether derivative which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording **2k** (570 mg, 62%) as a yellow oil; R_f=0.42 (20% EtOAc/80% hexane); IR (film) ν 2979, 2898, 1737, 1716, 1661, 1446, 1403, 1360, 1281, 1179, 1281, 1179, 1109, 1031, 975, 915, 878, 772, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.37–7.24 (m, 5H, Ar), 6.88 (td, J=15.6, 4.4 Hz, 0.6H, –C*H*=CHC(=O)), 6.77 (td, J=15.6, 4.0 Hz, 0.4H, C*H*=CH–C(=O)), 6.00 (td, J= 1.6, 16.0 Hz, 0.6H, CH=C*H*–C(=O)), 5.90 (td, J=2.0, 16.0 Hz, 0.4H, CH=C*H*–C(=O)), 5.56 (s, 0.5H, –NC*H*O), 5.44 (s, 0.5H, –NC*H*O), 5.27–5.10 (m, 2H, –CH_2Ph), 4.36 (ddd, J=16.0, 4.4, 2.0 Hz, 0.5H, –CH_2CH=CH), 4.28 (ddd, J=16.0, 4.4, 2.0 Hz, 0.5H, –CH_2CH=CH),4.22 (d, J= 7.2 Hz, 1H, –C*H*I), 4.16 (q, J=4.8 Hz, 2H, –OCH_2), 4.12–4.07 (m, 1H, –CH_2CH=CH), 3.76–3.41 (m, 2H, –NCH_2), 2.61–2.48 (m, 1H, –NCH_2CH_2), 1.6–1.9 (m, 1H, –NCH_2CH_2), 1.26 (t, J=7.2 Hz, 3H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 173.3, 166.2, 166.0, 155.8, 155.6, 154.7, 143.7, 143.2, 136.2, 136.0, 128.6, 128.5, 128.5, 128.3, 128.1, 128.0, 127.9, 127.7, 121.3, 121.1, 95.5, 95.41, 94.9, 94.9, 67.8, 67.5, 67.4, 67.3, 67.3, 67.2, 66.8, 60.3, 60.4, 60.3, 45.0, 44.8, 44.6, 33.8, 33.7, 32.8, 32.8, 31.0, 30.8, 26.8, 26.3, 26.1, 25.7, 25.1, 24.9, 14.2; FAB m/z calcd for ($C_{18}H_{22}INO_5+Na^+$): 481.98, found: 482.20.

4.3.5. *trans*-Benzyl-3-iodo-2-phenoxy-1-pyrrolidinecarboxylate (2l, Table 1, entry 12). Prepared following method B using **1a** (554 mg, 2.73 mmol), phenol (309 mg, 3.28 mmol) and *N*-iodosuccinimide (774 mg, 3.28 mmol) to yield the iodoether derivative which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording **2l** (0.667 g, 57%) as a colorless oil; R_f=0.51 (20% EtOAc/80% hexane); IR (film) ν 3063, 3033, 2954, 2896, 1716, 1596, 1488, 1455, 1407, 1354, 1284, 1210, 1186, 1117, 1079, 1053, 1027, 1002, 969, 917, 810, 752, 732, 692 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), rotamers, δ 7.43–7.06 (m, 7H, Ar), 7.04 (t, J=8.0 Hz, 2H, Ar), 6.9 (d, J=7.6 Hz, 1H, Ar), 6.23 (s, 0.5H, –NC*H*O), 6.10 (s, 0.5H, –NC*H*O), 5.24–5.10 (m, 2H, –CH_2Ph), 4.36 (dt, J=8.4, 4.8 Hz, 1H, –C*H*I), 3.84–3.69 (m, 2H, –NCH_2), 2.71–2.57 (m, 1H, –NCH_2CH_2), 2.23–1.32 (m, 1H, –NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.9, 155.9, 154.5, 153.9, 135.9, 135.7, 129.5, 128.3, 128.1, 127.9, 127.6, 127.2, 122.2, 122.1, 116.6, 116.5, 94.5, 94.1, 67.2, 67.1, 45.0, 44.8, 33.2, 32.4, 26.3, 25.5; HRMS (EI) m/z calcd for ($C_{18}H_{18}INO_3^+$): 423.0331, found: 423.0316.

4.3.6. 1-*tert*-Butyl-2-methyl-(2*S*,4*R*(*S*),5*S*(*R*))-5-(allyloxy)-4-iodo-1,2-pyrrolidenecarboxylate (2m and 2m′, Table 1, entry 13). Prepared following method B using **1c** (520 mg, 2.32 mmol), 3-buten-1-ol (473 µl, 6.96 mmol) and *N*-iodosuccinimide (550 mg, 2.34 mmol). Purification by flash chromatography (SiO_2, 10% EtOAc/90% hexane)

afforded the two diastereomers **2m**, **2m′** (835 mg, 88%) as colorless oils

4.3.7. 1-*tert*-Butyl-2-methyl-(2*S*,4*R*,5*S*)-5-(allyloxy)-4-iodo-1,2-pyrrolidenecarboxylate (2m, Table 1, entry 13). (480 mg, 57%); R_f=0.30 (4% EtOAc/96% hexane); $[\alpha]_D^{20}$=+48.39 (c=0.81 g/100 ml, $CHCl_3$); IR (film) ν 3080, 2977, 2952, 2931, 2869, 1760, 1719, 1647, 1478, 1456, 1438, 1377, 1314, 1259, 1169, 1062, 1014, 972, 934, 903, 875, 852, 804, 772, 750, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 5.94–5.84 (m, 1H, –C*H*=CH_2), 5.54 (s, 0.5H, –NC*H*O), 5.45 (s, 0.5H, –NC*H*O), 5.28 (s, 0.5H, –CH=CH_2), 5.23 (s, 0.5H, –CH=CH_2), 5.16–5.12 (m, 1H, –CH=CH_2), 4.64 (t, J=8.6 Hz, 0.5H, –NC*H*CO_2CH_3), 4.65 (t, J=8.44 Hz, 0.5H, –NC*H*CO_2CH_3), 4.54 (t, J=7.6 Hz, 0.5H, –NC*H*CO_2CH_3), 4.25–4.21 (m, 2H, –OCH_2), 4.10 (dd, J=12.4, 5.9 Hz, 0.5H, –C*H*I), 4.01 (dd, J=12.3, 5.5 Hz, 0.5H, –C*H*I), 3.71 (s, 3H, –OCH_3), 2.68–2.62 (m, 1H, CH_2CHI), 2.49 (dt, J=7.5, 17.8 Hz, 1H, –CH_2CHI), 1.48 (s, 4.5H, –C(CH_3)$_3$), 1.42 (s, 4.5H, –C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.2, 154.1, 134.4, 134.3, 117.0, 94.9, 94.5, 93.7, 81.6, 81.2, 70.9, 69.0, 68.3, 58.9, 58.2, 52.3, 52.2, 38.7, 37.9, 29.6, 28.3, 28.1, 25.6, 24.8; DEPT (100 MHz, $CDCl_3$), rotamers, δ 134.4(+), 117.0(−), 94.9(+), 94.5(+), 69.0(−), 68.3(−), 58.9(+), 58.2(+), 52.3(+), 52.2(+), 38.7(−), 37.9(−), 28.3(+), 28.1(+), 25.6(+), 24.8(+).

4.3.8. 1-*tert*-Butyl-2-methyl-(2*S*,4*S*,5*R*)-5-(allyloxy)-4-iodo-1,2-pyrrolidenecarboxylate (2m′, Table 1, entry 13). (355 mg, 43%); R_f=0.30 (7% EtOAc/93% hexane); $[\alpha]_D^{20}$=−56.38 (c=0.94 g/100 ml, $CHCl_3$); IR (film) ν 3080, 2928, 2858, 1763, 1714, 1647, 1478, 1456, 1437, 1375, 1323, 1296, 1258, 1166, 1122, 1053, 1011, 927, 904, 861, 843, 814, 772, 749, 700, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 5.89–5.85 (m, 1H, –C*H*=CH_2), 5.58 (s, 0.5H, –NC*H*O), 5.36 (s, 0.5H, –NC*H*O), 5.29 (s, 0.5H, –CH=CH_2), 5.25 (s, 0.5H, –CH=CH_2), 5.18 (1H, dd, J=9.8, 5.5 Hz, –CH=CH_2), 4.52 (d, J=9.7 Hz, 0.5H, –NC*H*CO_2CH_3), 4.43 (d, J=9.7 Hz, 0.5H, –NC*H*CO_2CH_3), 4.20–4.05 (m, 3H, –OCH_2 and –C*H*I), 3.74 (s, 3H, –OCH_3), 3.09–3.02 (m, 1H, –NCHCH_2), 2.48 (dd, J=15.0, 6.1 Hz, 1H, –NCHCH_2), 1.49 (s, 4.5H, –C(CH_3)$_3$), 1.42 (s, 4.5H, –C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 172.0, 171.4, 153.3, 134.4, 134.0, 117.7, 117.6, 116.5, 96.5, 96.3, 81.2, 81.0, 71.1, 70.6, 58.6, 58.1, 52.3, 52.1, 38.4, 37.2, 31.88, 29.6, 29.3, 28.3, 28.1, 22.6, 22.1, 20.7, 14.1; DEPT (100 MHz, $CDCl_3$), rotamers, δ δ 134.4(+), 134.0(+), 117.7(−), 96.5(+), 96.3(+), 71.1(−), 70.6(−), 58.6(+), 58.1(+), 52.3(+), 52.1(+), 38.4(−), 37.2(−), 29.6(−), 29.3(−), 28.3(+), 28.1(+), 22.1(+), 20.7(+).

4.4. Method C. General procedure for iodocarbamation

A solution of I_2 (1.2 mequiv) in dry THF was added dropwise to a stirred solution of the *N*-[(benzyloxy)carbonyl]-2-pyrrolidine **1a** (1.0 mequiv) and the corresponding carbamate (1 or 2 mequiv) in dry THF at −78 °C and under nitrogen. The resulting mixture was stirred for 10 min and then water and dichloromethane were added. The organic phase was separated and the aqueous phase washed with dichloromethane. The combined organic layers were washed with a $Na_2S_2O_3$ (0.5 M), and with saturated aqueous Na_2CO_3. The organic phase was dried over Na_2SO_4 and the solvent removed under vacuo. Purification by column chromatography afforded the 3-iodo-2-carbamate pyrrolidine derivative **3**.

4.4.1. Benzyl 2-[(*tert*-butoxycarbonyl)amino]-3-iodo-1-pyrrolidinecarboxylate (3a, Table 2, entry 1). Prepared following method C using **1a** (203 mg, 1 mmol), *tert*-butylcarbamate (119 mg, 1 mmol) and iodine (305 mg, 1.2 mmol) to yield the iodocarbamate derivative which was purified by flash chromatography (SiO_2, 30% EtOAc/70% hexane) affording a *trans*/*cis* mixture of **3a** (72/28) (332 mg, 74%) as an orange foam; R_f=0.46 (30% EtOAc/70% hexane); IR (film) $\nu_{máx}$ 3320, 2978, 1696, 1499, 1412, 1365, 1280, 1249, 1158, 1117, 1050, 1025, 974, 910, 771, 731, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.26–7.19 (m, 5H, Ar), 5.66–5.55 (m, 1H, –NC*H*N–), 5.26 (br, 1H, –N*H*), 5.20–5.04 (m, 2H, –CH_2Ph), 4.36–4.24 (m, 1H, –C*H*I), 3.63–3.45 (m, 2H, –NC$H_2$$CH_2$), 2.31–2.01 (m, 2H, –$NCH_2CH_2$), 1.32 (br, 9H, –C(C$H_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.3, 153.9, 136.3, 128.5, 128.1, 127.9, 127.8, 127.4, 80.3, 75.7, 74.6, 67.2, 45.3, 33.8, 33.0, 28.3, 27.1; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.5(+), 128.1(+), 127.9(+), 127.8(+), 127.4(+), 80.3(+), 75.7(+), 74.6(+), 67.2(−), 45.3(−), 33.8(−), 33.0(−), 28.3(+), 27.1(+); ^1H NMR (400 MHz, d_2-tetrachloroethane, T=360 K), rotamers, δ 7.39–7.35 (m, 5H, Ar), 5.67 (d, J=5.6 Hz, 0.73H, –NC*H*N–), 5.56 (d, J=6.0 Hz, 0.27H, –NC*H*N–), 5.27–5.2 (m, 2H, –CH_2Ph), 4.9 (d, J=4.3 Hz, 1H, –N*H*), 4.72 (s, 0.27H, –C*H*I), 4.46 (d, J=4.0 Hz, 0.73H, –C*H*I), 3.83–3.72 (m, 1H, –NC$H_2$$CH_2$), 3.63–3.54 (m, 1H, –NC$H_2$$CH_2$), 2.31–2.01 (m, 2H, –$NCH_2CH_2$), 1.48 (br, 9H, –C(C$H_3$)$_3$); HRMS (EI) *m*/*z* calcd for ($C_{17}H_{23}IN_2O_4$): 447.0703, found: 447.0791.

4.4.2. Benzyl 2-[(benzyloxycarbonyl)amino]-3-iodo-1-pyrrolidinecarboxylate (3b, Table 2, entry 2). Prepared following method C using **1a** (340 mg, 1.67 mmol), benzyl carbamate (504 mg, 3.34 mmol) and iodine (509 mg, 2.0 mmol) to yield the iodocarbamate derivative which was purified by flash chromatography (SiO_2, 1:4:4, EtOAc:Hex:$CHCl_3$), followed by preparative thin layer chromatography (40% EtOAc/60% hexane) affording a *trans*/*cis* mixture (77/23) of **3b** (569 mg, 71%) as an orange foam; R_f=0.5 (30% EtOAc/70% hexane); IR (film) ν 3304, 3062, 3032, 2953, 2893, 1693, 1586, 1518, 1454, 1410, 1351, 1279, 1244, 1205, 1177, 1116, 1045, 1027, 976, 914, 870, 772, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.26–7.19 (m, 10H, Ar), 5.66 (d, J=6.6 Hz, 0.45H, –NC*H*N–), 5.64 (s, 0.55H, –NC*H*N–), 5.33 (br, 0.45H, –N*H*), 5.29 (br, 0.55H, N*H*), 5.09–5.47 (m, 4H, 2×–CH_2Ph), 4.39 (br, 0.45H, –C*H*I), 4.28 (br, 0.55H, –C*H*I), 3.66–3.59 (m, 1H, –NC$H_2$$CH_2$), 3.51–3.41 (m, 1H, –NC$H_2$$CH_2$), 2.30–2.20 (m, 1H, –$NCH_2CH_2$), 2.07 (dd, J=13.9, 5.6 Hz, 1H, –NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.5, 154.3, 136.2, 136.0, 128.6, 128.3, 128.0, 127.9, 127.6, 75.7, 74.9, 67.3, 67.0, 45.4, 34.1, 33.1, 27.2. 26.3; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.6(+), 128.3(+), 128.3(+), 128.0(+) 127.9(+), 127.6(+), 75.7(+), 74.8(+), 67.3(−), 67.0(−), 45.4(−), 34.1(−), 33.1(−), 27.2(+), 26.3(+).

4.4.3. Benzyl-3-iodo-2-[(methoxycarbonyl)amino]-1-pyrrolidinecarboxylate (3c, Table 2, entry 3). Prepared following method C using **1a** (3.41 g, 16.8 mmol), methyl carbamate (2.6 g, 33.6 mmol) and iodine (5.12 g, 20.2 mmol) to yield the iodocarbamate derivative which was purified by flash chromatography (SiO_2, 40% EtOAc/60% hexane). The excess carbamate was further removed washing with Et_2O/hexane (20%/80%) to affording a *trans*/*cis* mixture (73/27) of **3c** (4.76 g, 70%) as an orange foam; R_f=0.26 (30% EtOAc/70% hexane); IR (film) ν 3301, 2954, 2885, 1703, 1699, 1694, 1683, 1520, 1418, 1353, 1250, 1179, 1114.6, 1044, 772, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.37–7.28 (m, 5H, Ar), 5.73–5.67 (m, 1H, –NC*H*N–), 5.58 (br, 1H, –N*H*), 5.21–5.10 (m, 2H, –CH_2Ph), 4.46 (br, 0.27H, –C*H*I), 4.34 (br, 0.73H, –C*H*I), 3.75–3.54 (m, 5H, –NCH_2 and –OCH_3), 2.43–2.37 (m, 1H, –NCH$_2$CH_2), 2.35–2.14 (m, 1H, –NCH$_2$CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.3, 154.5, 136.4, 128.7, 128.4, 128.3, 128.1, 127.9, 76.0, 75.1, 67.6, 52.5, 45.6, 34.5, 33.4, 27.2, 26.1; HRMS (EI) *m*/*z* calcd for ($C_{14}H_{17}IN_2O_4$+H^+) requires: 405.0311, found: 405.0314.

4.4.4. Benzyl-3-iodo-2-{[(4-methylphenyl)sulfonyl]-amino}-1-pyrrolidinecarboxylate (3d, Table 2, entry 4). Prepared following method C using **1a** (335 mg, 1.65 mmol), 4-methylbenzenesulfonamide ($TsNH_2$; 565 mg, 3.3 mmol) and iodine (503 mg, 1.98 mmol) to yield the iodocarbamate derivative which was purified by flash chromatography (SiO_2, 40% EtOAc/60% hexane) affording a *trans*/*cis* mixture (69/31) of **3d** (258 mg, 32%) as a white solid which decomposed within a few days at 4 °C; R_f=0.26 (30% EtOAc/70% hexane); IR (film) ν 3250, 1701, 1698, 1597, 1496, 1410, 1337, 1278, 1161, 1118, 1094, 1038, 916, 814, 771, 733, 697, 667, 576, 542 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.79 (d, J=8.2 Hz, 2H, Ar), 7.66 (d, J=7.7 Hz, 1H, Ar), 7.32–7.10 (m, 7H, Ar), 5.67–5.65 (m, 1H, –NC*H*N–), 5.23–4.97 (m, 2H, –CH_2Ph), 4.69 (br, 0.31H, –C*H*I), 4.66 (br, 1H, –N*H*), 4.50 (d, J= 4.4 Hz, 0.69H, –C*H*I), 3.64–3.46 (m, 2H, –NCH_2), 2.57–2.29 (m, 1H, –NCH$_2$CH_2), 2.41 (s, 2.07H, Ar-CH_3), 2.34 (s, 0.93H, Ar-CH_3), 2.10 (dd, J=14.4, 5.6 Hz 1H, –NCH$_2$CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.1, 144.3, 143.7, 139.4, 136.5, 136.2, 130.0, 129.9, 128.7, 128.4, 128.3, 127.9, 127.7, 127.6, 127.4, 126.6, 67.7, 67.4, 45.5, 34.0, 32.7, 28.0, 26.4, 21.8, 21.7.

4.4.5. Benzyl-2-[(*tert*-butoxycarbonyl)amino]-3-iodo-1-piperidinecarboxylate (3e, Table 2, entry 5). Prepared following method C using benzyl 3,4-dihydro-1(2*H*)-pyridinecarboxylate **1d** (166 mg, 0.77 mmol), *tert*-butyl-carbamate (184 mg, 1.54 mmol) and iodine (196 mg, 0.77 mmol) to yield the iodocarbamate derivative which was purified by flash chromatography (SiO_2, 30% EtOAc/70% hexane) affording **3e** (0.57 mmol, 75%) as a colorless oil; R_f=0.3 (20% EtOAc/80% hexane); IR (film) ν 3485, 3323, 2976, 1694, 1597, 1515, 1423, 1165, 874, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.38–7.27 (m, 5H, Ph), 6.02 (d, J=6.4 Hz, 1H, –NC*H*N), 5.21–5.13 (m, 2H, –CH_2Ph), 4.83 (br, 1H, –N*H*), 4.52 (br, 1H, –C*H*I), 4.07 (d, J=11.2 Hz, 1H, –NCH_2CH$_2$), 3.0 (br, 1H, –NCH_2CH$_2$), 2.02–1.92 (m, 4H, –NCH$_2$(CH_2)$_2$CHI–), 1.42 (s, 9H, –C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.1, 136.4, 128.3, 127.8, 127.6, 80.7, 79.4, 67.4, 65.1, 39.2, 29.6, 28.2, 21.2; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.3(+), 127.8(+), 127.6(+), 80.7(−), 67.4(−), 65.1(+), 39.2(−), 29.6(+), 28.2(+), 21.2(−); HRMS (EI) *m*/*z* calcd for ($C_{18}H_{25}IN_2O_4$+H^+): 461.0859, found: 461.0937.

4.5. Method D. General procedure for radical cyclizations

Iodoether derivative **2** (1.0 mequiv) in dry *t*-BuOH was added dropwise to a stirred mixture of $NaCNBH_3$ (1.2 mequiv), Bu_3SnH (0.05 mequiv) and AIBN (0.1 mequiv) in dry *t*-BuOH under nitrogen at 80 °C. After refluxing for 14 h the mixture was cooled to rt. Three portions of benzene were added and the azeotropic mixture was removed under reduced pressure. The residue was taken up in dichloromethane and filtered through celite. The solvent was removed in vacuo to yield the bicyclic derivative **4**, which was purified by flash column chromatography.

4.5.1. Benzyl-3-methylenehexahydro-6*H*-furo[2,3-*b*]pyrrole-6-carboxylate (4a, Table 3, entry 1). Prepared following method D using **2a** (400 mg, 1.04 mmol), $NaCNBH_3$ (82 mg, 1.25 mmol), Bu_3SnH (15 μl, 0.05 mmol) and AIBN (17.4 mg, 0.104 mmol) to yield the bicyclic derivative which was purified by flash column chromatography (SiO_2, 20% EtOAc/80% hexane) affording **4a** (192 mg, 71%) as a colorless oil; R_f=0.36 (20% EtOAc/80% hexane); IR (film) ν 2953, 1710, 1411, 1356, 1272, 1171, 1114, 1058, 1025, 888, 770, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), rotamers, δ 7.36–7.24 (m, 5H, Ar), 5.89–5.84 (m, 1H, –NC*H*O), 5.26–5.02 (m, 4H, –CH_2Ph and –C=CH_2), 4.4 (s, 2H, –OCH_2), 3.68–3.63 (m, 1H, –NCH_2), 3.42–3.29 (m, 2H, –CH$_2$C*H* and –NCH_2), 2.07–1.84 (m, 2H, –NCH$_2$CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.4, 154.2, 149.5, 136.5, 136.3, 128.2, 127.7, 127.6, 127.5, 105.4, 92.8, 92.2, 70.9, 66.7, 47.3, 46.4, 45.4, 45.2, 30.8, 30.4; HRMS (EI) *m*/*z* calcd for ($C_{15}H_{17}NO_3^+$): 259.1208, found: 259.1195.

4.5.2. Benzyl-4-methylene hexahydropyrano[2,3-*b*]pyrrole-7(2*H*)-carboxylate (4b, Table 3, entry 2). Prepared following method D using **2b** (261 mg, 0.65 mmol), $NaCNBH_3$ (52 mg, 0.78 mmol), Bu_3SnH (9 μl, 0.033 mmol) and AIBN (10 mg, 0.065 mmol) to yield the bicyclic derivative which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording **4b** (83 mg, 46%) as a colorless oil; R_f=0.53 (20% EtOAc/80% hexane); IR (film) ν 3067, 3033, 2954, 1713, 1651, 1498, 1450, 1415, 1354, 1285, 1271, 1256, 1235, 1178, 1121, 1085, 1055, 987, 922, 798, 771, 736, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), rotamers, δ 7.37–7.25 (m 5H, Ar), 5.29–5.26 (m, 1H, –NC*H*O), 5.19–5.03 (m, 2H, –CH_2Ph), 4.88–4.84 (m, 2H, C=CH_2), 4.00–3.95 (m, 1H, –NCH_2), 3.67–3.62 (m, 1H, –OCH_2), 3.46–3.35 (m, 2H, –OCH_2 and –NCH_2), 2.70–2.64 (m, 1H, –OCH$_2$CH_2), 2.46 (dt, J=14.0, 5.6 Hz, 1H, C*H*C=CH$_2$), 2.24–2.16 (m, 1H, –OCH$_2$CH_2), 2.07–2.03 (m, 1H, –NCH$_2$CH_2), 1.89–1.82 (m, 1H, and –NCH$_2$CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.9, 154.7, 154.3, 143.1, 137.1, 136.7, 136.4, 128.4, 128.4, 128.3, 128.0, 127.8, 127.8, 127.7, 111.7, 111.6, 110.3, 89.6, 86.7, 86.2, 67.0, 66.9, 66.5, 66.4, 65.4,

65.3, 47.3, 46.5, 46.2, 45.8, 45.5, 31.5, 30.5, 29.5, 27.7, 26.8, 25.7, 24.9; HRMS (EI) *m/z* calcd for ($C_{16}H_{19}NO_3^+$): 273.1365, found: 273.1371; and the corresponding reduced product benzyl-2-(3-butynyloxy)-1-pyrrolidinecarboxylate (66 mg, 37%) as a colorless oil; R_f=0.44 (20% EtOAc/80% hexane); IR (film) ν 3296, 2955, 1714, 1640, 1506, 1456, 1404, 1382, 1288, 1180, 1102, 970, 917, 754, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.35–7.24 (m, 5H, Ar), 5.33 (d, J=4.8 Hz, 0.5H, –NC*H*O), 5.22 (d, J=5.2 Hz, 0.5H, –NC*H*O), 5.20–5.08 (m, 2H, –CH_2Ph), 3.75–3.67 (m, 1H, –NCH_2), 3.58–3.48 (m, 2H, –OCH_2), 3.40–3.33 (m, 1H, –NCH_2), 2.43 (tt, J=6.8, 2.4 Hz, 1H, –CH_2–C≡CH), 2.40 (dt, J=6.8, 4.4 Hz, 1H, –CH_2–C≡CH), 2.30–2.08 (m, 1H, –C≡C*H*), 2.07–1.73 (m, 4H, –NCH$_2$CH_2 and –NCH$_2$CH$_2$CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ, 155.7, 154.7, 136.6, 136.3, 128.5, 128.2, 128.1, 128.0, 127.8, 87.9, 87.3, 87.5, 81.5, 81.2, 69.2, 69.0, 67.2, 66.9, 66.3, 65.8, 46.0, 45.8, 32.9, 32.4, 22.6, 21.7, 20.0, 19.8.

4.5.3. Benzyl-2-methyl-3-methylenehexahydro-6*H*-furo[2,3-*b*]pyrrole-6-carboxylate (4c, Table 3, entry 3). Prepared following method D using **2c** (180 mg, 0.45 mmol), $NaCNBH_3$ (35.6 mg, 0.54 mmol), Bu_3SnH (6.2 µl, 0.023 mmol) and AIBN (8 mg, 0.05 mmol) to yield the bicyclic derivative which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording **4c** (75 mg, 61%) as a colorless oil; R_f=0.63 (20% EtOAc/80% hexane); IR (film) ν 2974, 2875, 1716, 1447, 1418, 1356, 1322, 1274, 1208, 1176, 1112, 1073, 1001, 900, 771, 737, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), rotamers, δ 7.39–7.24 (m, 5H, Ar), 5.88–5.72 (m, 1H, –NC*H*O), 5.32–5.28 (m, 1H, –C=CH_2), 5.26–4.91 (m, 3H, –CH_2Ph and C=CH_2), 4.55–4.52 (m, 1H, –OC*H*), 3.72–3.55 (1H, m, –NCH_2), 3.43–3.29 (m, 3H, –NCH_2 and C*H*C=CH$_2$), 2.11–2.02 (m, 1H, –NCH$_2$CH_2), 1.89–1.80 (m, 1H, –NCH$_2$CH_2), 1.33–1.28 (m, 3H, –CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.8, 154.6, 154.4, 154.3, 154.2, 136.8, 136.4, 128.3, 128.0, 127.8, 105.7, 105.4, 105.2, 91.0, 90.5, 90.4, 77.9, 77.8, 76.4, 66.9, 66.8, 48.0, 47.1, 47.0, 45.6, 45.3, 45.1, 45.0, 31.8, 31.5, 30.8, 30.0, 20.9, 20.6, 19.9, 19.8; HRMS (EI) *m/z* calcd for ($C_{16}H_{19}NO_3^+$): 273.1365, found: 273.1354.

4.5.4. Benzyl-(3*Z*)-ethylidinehexahydro-6*H*-furo[2,3-*b*]pyrrole-6-carboxylate (4d, Table 3, entry 4). Prepared following method D using **2d** (140 mg, 0.35 mmol), $NaCNBH_3$ (63 mg, 0.42 mmol), Bu_3SnH (5 µl, 0.02 mmol) and AIBN (7 mg, 0.04 mmol) to yield the bicyclic derivative which was purified by flash column chromatography (SiO_2, 20% EtOAc/80% hexane) affording **4d** (69.0 mg, 74%) as a colorless oil; R_f=0.31 (20% EtOAc/80% hexane); IR (film) ν 2952, 1715, 1498, 1411, 1352, 1272, 1170, 1115, 882, 771, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), rotamers, δ 7.37–7.26 (m, 5H, Ar), 5.88–5.85 (m, 1H, –NC*H*O), 5.44–5.01 (m, 3H, –CH_2Ph and –C=C*H*CH$_3$), 4.44–4.31 (m, 2H, –OCH_2), 3.66–3.27 (m, 3H, –NCH_2 and C*H*C=CHCH$_3$), 2.10–1.80 (m, 2H, NCH$_2$CH_2), 1.64 (d, 1.5H, =CHCH_3), 1.59 (dd, J=5.4, 1.8 Hz, 1.5H, =CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.5, 140.9, 136.8, 128.3, 127.9, 127.7, 116.2, 115.6, 110.3, 93.0, 92.8, 92.4, 92.2, 71.1, 68.9, 66.9, 66.8, 47.3, 46.4, 45.5, 45.3, 44.4, 43.5, 31.3, 30.9, 29.9, 29.4, 14.7, 14.4; HRMS (EI) *m/z* calcd for ($C_{16}H_{19}NO_3^+$): 273.1365, found: 273.1352.

4.5.5. 6-Acetyl-3-methylenehexahydro-2*H*-furo[2,3-*b*]pyrrole (4e, Table 3, entry 5). Prepared following method D using **2e** (1.08 g, 3.69 mmol), $NaCNBH_3$ (292 mg, 4.43 mmol), Bu_3SnH (50 µl, 0.18 mmol) and AIBN (62 mg, 0.4 mmol) to yield the bicyclic derivative which was purified by flash column chromatography (SiO_2, 60% EtOAc/40% hexane) affording **4e** (464 mg, 75%) as a colorless oil; R_f=0.19 (60% EtOAc/40% hexane); IR (film) ν 3079, 2951, 2876, 1657, 1417, 1348, 1208, 1169, 1051, 972, 895 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 5.78 (d, J=6.0 Hz, 0.15H, –NC*H*O), 5.55 (d, J=5.6 Hz, 0.85H, –NC*H*O), 4.89–4.83 (m, 2H, –C=CH_2), 4.21–4.18 (m, 2H, –OCH_2), 3.59–3.53 (m, 1H, –NCH_2), 3.38–3.29 (m, 0.3H, C*H*C=CH$_2$), 3.20–3.18 (m, 1H, –NCH_2), 3.11–3.04 (m, 0.7H, C*H*C=CH$_2$),1.96 (s, 2.6H, CHCH_3), 1.91–1.70 (m, 2.4H, CHCH_3 and N–CH$_2$–CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 170.0, 169.5, 149.1, 149.8, 105.5, 105.3, 92.7, 90.9, 70.8, 70.6, 70.5, 47.6, 47.4, 46.4, 45.7, 44.1, 30.6, 29.1, 22.5, 21.3; DEPT (100 MHz, $CDCl_3$), rotamers, δ 105.3(−), 92.7(+), 90.9(+), 70.8(−), 70.6(−), 70.5(+), 47.6(+), 47.4(+), 46.4(+), 45.7(−), 44.1(−), 30.6(−), 29.1(−), 22.5(+), 21.3(+); HRMS (EI) *m/z* calcd for ($C_9H_{13}NO_3^+$): 167.0946, found: 167.0945.

4.5.6. 6-*tert*-Butyl 5-methyl (3a*R*,5*S*,6a*S*)-3-methylenehexahydro-6*H*-furo[2,3-*b*]pyrrole-5,6-dicarboxylate (4g, Table 3, entry 6) and 6-*tert*-butyl 5-methyl (3a*S*,5*S*,6a*R*)-3-methylenehexahydro-6*H*-furo[2,3-*b*]pyrrole-5,6-dicarboxylate (4g′, Table 3, entry 6). Prepared following method D using a mixture of diastereomers **2g′** (240 mg, 0.59 mmol), $NaCNBH_3$ (46 mg, 0.71 mmol), Bu_3SnH (8 µl, 0.03 mmol) and AIBN (10 mg, 0.06 mmol) to yield the two bicyclic diastereomers. Purification by flash chromatography (SiO_2, 10% EtOAc/90% hexane) afforded the two diastereomers **4g** and **4g′** (101 mg, 61%) as a colorless oil.

4.5.7. 6-*tert*-Butyl 5-methyl (3a*R*,5*S*,6a*S*)-3-methylenehexahydro-6*H*-furo[2,3-*b*]pyrrole-5,6-dicarboxylate (4g, Table 3, entry 6). (46 mg, 46%); R_f=0.3 (20%EtOAc/80% hexane); $[\alpha]_D^{20}$=−112.54 ($CDCl_3$, c=1.18 g/100 ml); IR (film) ν 2976, 1749, 1706, 1477, 1455, 1436, 1392, 1366, 1301, 1257, 1204, 1366, 1301, 1257, 1204, 1163, 1132, 1063, 1044, 1022, 980, 917, 856, 778, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 5.79 (d, J=5.4 Hz, 0.6H, –NC*H*O), 5.60 (d, J=5.2 Hz, 0.4H, –NC*H*O), 4.93 (s, 1H, –C=CH_2), 4.87 (s, 1H, –C=CH_2), 4.47–4.44 (m, 1H, NC*H*CO$_2$CH$_3$), 4.37–4.25 (m, 2H, –OCH_2), 3.65 (s, 3H, CO$_2$CH_3), 3.25 (br, 1H, –C*H*C=CH$_2$), 2.15–2.10 (m, 2H, –NCHCH_2), 1.41 (s, 4H, –C(CH_3)$_3$), 1.33 (s, 5H, –C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 172.8, 172.6, 153.9, 153.3, 148.6, 148.5, 106.0, 93.2, 93.9, 81.1, 81.0, 70.6, 70.4, 60.8, 60.4, 52.2, 52.1, 46.8, 45.8, 34.6, 33.9, 28.2, 28.1; DEPT (100 MHz, $CDCl_3$), rotamers, δ 106.0(−), 93.2(+), 93.9(+), 70.6(−), 70.4(−), 60.8(+), 60.4(+), 52.2(+), 52.1(+), 46.8(+), 45.8(+), 34.6(−), 33.9(−), 28.2(+), 28.1(+).

4.5.8. 6-*tert*-Butyl 5-methyl (3a*S*,5*S*,6a*R*)-3-methylenehexahydro-6*H*-furo[2,3-*b*]pyrrole-5,6-dicarboxylate (4g′, Table 3, entry 6). (55 mg, 54%); R_f=0.3 (20%

EtOAc/80% hexane); $[\alpha]_D^{20}=+106.06$ ($CDCl_3$, $c=0.664$ g/100 ml); IR (film) ν 2953, 1755, 1706, 1456, 1436, 1392, 1366, 1280, 1257, 1164, 1122, 1069, 1053, 1034, 1008, 981, 937, 918, 890, 847, 808, 773, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 5.81 (d, $J=5.2$ Hz, 0.5H, –NC*H*O), 5.74 (d, $J=4.9$ Hz, 0.5H, –NC*H*O), 4.91 (d, $J=0.9$ Hz, 1H, –C=CH_2), 4.87 (d, $J=1.9$ Hz, 1H, C=CH_2), 4.53 (d, $J=1.5$ Hz, 0.5H, –NC*H*CO_2CH_3), 4.49 (d, $J=1.3$ Hz, 0.5H, –NC*H*CO_2CH_3), 4.39–4.25 (m, 2H, –OCH_2), 3.58 (s, 3H, –CO_2CH_3), 3.18 (br, 1H, –C*H*C=CH_2), 2.41–2.37 (m, 1H, –NCHCH_2), 2.13–2.10 (br, 1H, –NCHCH_2), 1.41 (s, 4.5H, –C(CH_3)$_3$), 1.34 (s, 4.5H, –C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.0, 149.9, 105.8, 93.7, 80.8, 70.9, 59.3, 58.7, 52.0, 46.9, 46.0, 34.4, 34.0, 29.7, 28.2.

4.5.9. Benzyl-3-methylhexahydro-6*H*-furo[2,3-*b*]pyrrole-6-carboxylate (4h, Table 3, entry 7). Prepared following method D using **2h** (162 mg, 0.42 mmol), $NaCNBH_3$ (36 mg, 0.50 mmol), Bu_3SnH (7 μl, 0.02 mmol) and AIBN (8 mg, 0.05 mmol) to yield the bicyclic derivative which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording a mixture of isomers *endo*/*exo* (95:5) **4h** (88 mg, 92%) as a white solid; mp: 42–44 °C; $R_f=0.45$ (20% EtOAc/80% hexane); IR (film) ν 2960, 2877, 1712, 1497, 1455, 1409, 1353, 1309, 1258, 1213, 185, 1118, 1096, 1050, 1006, 907, 677, 773, 737, 698, 512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.37–7.23 (m, 5H, Ar), 5.74 (d, $J=4.8$ Hz, 0.5H, –NC*H*O), 5.68 (d, $J=5.2$ Hz, 0.5H, –NC*H*O), 5.30–5.24 (m, 0.6H, –CH_2Ph), 5.12–5.04 (m, 1.4H, –CH_2Ph), 3.92–3.88 (t, $J=7.5$ Hz, 1H, –OCH_2), 3.54–3.37 (m, 3H, –OCH_2 and –NCH_2), 2.76–2.72 (m, 1H, C*H*CHCH_3), 2.41–2.39 (m, 1H, CHC*H*CH_3), 1.98–1.72 (m, 2H, NCH_2CH_2), 1.02 (d, $J=6.8$ Hz, 0.15H, CHCH_3), 0.96 (d, $J=6.8$ Hz, 2.85H, CHCH_3); ^1H NMR (400 MHz, d_2-tetrachloroethane, $T=350$ K) δ 7.42–7.35 (m, 5H, Ar), 5.78 (d, $J=5.4$ Hz, 1H, –NC*H*O), 5.26–5.17 (m, 2H, –CH_2Ph), 3.95 (t, $J=7.8$ Hz, 1H, –OCH_2), 3.55 (t, $J=7.8$ Hz, 2H, –NCH_2), 3.45 (t, $J=9.6$ Hz, 1H, –OCH_2), 2.83–2.76 (m, 1H, C*H*CHCH_3), 2.52–2.40 (m, 1H, CHC*H*CH_3), 1.96–1.72 (m, 2H, NCH_2CH_2), 1.11 (d, $J=6.8$ Hz, 0.15H, CHCH_3), 1.05 (d, $J=6.8$ Hz, 2.85H, CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.5, 136.6, 128.3, 127.7, 93.1, 92.4, 72.5, 66.8, 47.2, 46.9, 46.7, 45.7, 35.6, 23.2, 22.4, 10.9; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.3(+), 127.7(+), 93.1(+), 92.4(+), 72.5(−), 66.8(−), 47.2(−), 46.9(−), 46.7(+), 45.7(+), 35.6(+), 23.2(−), 22.4(−), 10.9(+); HRMS (EI) *m*/*z* calcd for ($C_{15}H_{19}NO_3$): 261.1365, found: 261.1372.

4.5.10. Benzyl-4-methylhexahydropyrano[2,3-*b*]pyrrole-7(2*H*)carboxylate (4i, Table 3, entry 8). Prepared following method D using **2i** (302 mg, 0.75 mmol), $NaCNBH_3$ (59 mg, 0.9 mmol), $SnBu_3H$ (10 μl, 0.04 mmol) and AIBN (12 mg, 0.07 mmol) to yield the bicyclic derivative **4i** which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording a mixture of *endo*/*exo* isomers (40:60) (63 mg, 30%) as a colorless oil; $R_f=0.16$ (10% EtOAc/90% hexane); IR (film) ν 2954, 1712, 1453, 1411, 1352, 1271, 1213, 1185, 1116, 1077, 991, 971, 920, 771, 751, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.35–7.26 (m, 5H, Ar), 5.30–5.03 (m, 3H, –NC*H*O, –CH_2Ph), 3.92–3.30 (m, 4H, –OCH_2 and –NCH_2), 2.14–1.58 (m, 5H, –CHC*H*CH_3, –NCH_2CH_2 and –OCH_2CH_2), 1.48–1.30 (m, 1H, C*H*CHCH_3), 1.19–1.14 (m, 2H, CHCH_3), 0.96–0.90 (m, 1H, CHCH_3); ^1H NMR (400 MHz, d_2-tetracloroethane, $T=385$ K) δ 7.40–7.31 (m, 5H, Ar), 5.27 (d, $J=4.0$ Hz, 0.6H, –NC*H*O), 5.20 (br, 2H, –CH_2Ph), 5.12 (d, $J=2.2$ Hz, 0.4H, –NC*H*O), 3.89–3.86 (m, 4H, –OCH_2 and –NCH_2), 2.14–1.79 (m, 4H, –C*H*CHCH_3, –NCH_2CH_2 and –CHC*H*CH_3), 1.50–1.22 (m, 2H, –OCH_2CH_2), 1.20 (d, $J=7.2$ Hz, 1.8H, –CHCH_3), 1.02 (d, $J=6.4$ Hz, 1.2H, –CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.8, 154.4, 136.8, 136.5, 128.4, 128.3, 127.9, 127.8, 127.7, 85.8, 85.38, 82.9, 82.5, 66.8, 66.7, 65.3, 65.2, 60.5, 45.4, 45.2, 45.0, 44.8, 44.1, 43.3, 29.6, 29.5, 29.1, 28.5, 28.4, 27.4, 27.0, 26.6, 25.8, 21.3, 20.4, 20.04, 19.3, 16.4, 13.5; HRMS (EI) *m*/*z* calcd for ($C_{16}H_{21}NO_3^+$): 275.1521, found: 275.1521; and the corresponding reduced product benzyl-2-(3-butenyloxy)-1-pyrrolidinecarboxylate (13 mg, 6%) as a colorless oil; $R_f=0.37$ (10% EtOAc/90% hexane); ^1H NMR (200 MHz, $CDCl_3$), rotamers, δ 7.39–7.26 (m, 5H, Ar), 5.75 (br, 1H, CH_2-C*H*=CH_2), 5.14 (br, 5H, –NC*H*O, –CH_2Ph and CH_2-CH=CH_2), 3.53–3.43 (m, 4H, –NCH_2 and –OCH_2), 2.4–1.62 (m, 4H, NCH_2CH_2 and CH_2CH=CH_2); and benzyl-1-pyrrolidinecarboxylate (30 mg, 20%) as a colorless oil; $R_f=0.24$ (10% EtOAc/90% hexane); ^1H NMR (200 MHz, $CDCl_3$), rotamers, δ 7.36–7.15 (m, 5H, Ar), 5.14 (s, 2H, –CH_2Ph), 3.42–3.35 (m, 4H, –N(CH_2)$_2$), 1.86–1.79 (m, 4H, –N(CH_2CH_2)$_2$).

4.5.11. Benzyl-3-benzylhexahydro-6*H*-furo[2,3-*b*]pyrrole-6-carboxylate (4j, Table 3; entry 9). Prepared following method D using **2j** (1.06 g, 2.23 mmol), $NaCNBH_3$ (181 mg, 2.75 mmol), Bu_3SnH (31 μl, 0.11 mmol) and AIBN (46 mg, 0.02 mmol) to yield the bicyclic derivative which was purified by flash column chromatography (SiO_2, dichloromethane) affording a mixture of isomers *endo*/*exo*-**4j** (74:26) (510 mg, 66%) as a colorless oil; $R_f=0.16$ (dichloromethane); IR (film) ν 2941, 2875, 1712, 1602, 1500, 1454, 1410, 1353, 1278, 1213, 1187, 1091, 1038, 1006, 917, 748, 600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.37–7.16 (m, 10H, Ar), 5.75–5.70 (m, 1H, –NC*H*O), 5.32–5.08 (m, 2H, –(C=O)CH_2Ph), 3.92–3.90 (m, 1H, –OCH_2), 3.67–3.62 (m, 2H, –NCH_2), 3.48–3.43 (m, 1H, –OCH_2), 2.72–2.66 (m, 4H, C*H*CHCH_2Ph, CHC*H*CH_2Ph and CHCH_2Ph), 1.99–1.83 (m, 2H, –NCH_2CH_2); ^1H NMR (400 MHz, toluene, $T=370$ K) δ 7.38–6.93 (m, 10H, Ar), 5.78 (d, $J=5.8$ Hz, 0.24H, –NC*H*O), 5.71 (d, $J=5.04$ Hz, 0.76H, –NC*H*O), 5.17 (s, 2H, –(C=O)CH_2Ph), 3.78–3.71 (m, 1H, –OCH_2), 3.51–3.29 (m, 3H, –OCH_2 and –NCH_2), 2.48–2.32 (m, 3.52H, –CHCH_2Ph, C*H*CHCH_2Ph and CHC*H*CH_2Ph), 2.27–2.23 (m, 0.24H, C*H*CHCH_2Ph), 2.02–1.99 (m, 0.24H, CHC*H*CH_2Ph), 1.72–1.63 (m, 0.76H, CH_2CH_2N), 1.62–1.57 (m, 0.24H, –NCH_2CH_2), 1.51–1.39 (m, 0.76H, NCH_2CH_2), 1.32–1.27 (m, 0.24H, NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.0, 154.5, 139.8, 139.6, 128.7, 128.5, 128.4, 128.2, 127.9, 127.8, 126.2, 93.1, 92.4, 71.7, 71.0, 66.9, 47.2, 46.9, 45.6, 44.6, 43.3, 33.2, 23.3, 22.5; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.7(+), 128.5(+), 128.4,(+) 128.2(+),127.9(+), 127.8(+), 126.2(+), 93.1(+), 92.4(+), 71.7(−), 71.0(−), 66.9 (−), 47.2(−), 46.9(−), 45.6(+), 44.6(+), 43.3(+), 33.2(−),

23.3(−), 22.5(−); HRMS (EI) *m/z* calcd for ($C_{21}H_{23}NO_3^+$): 337.1678, found: 337.1696.

4.5.12. Benzyl-3-(2-ethoxy-2-oxoethyl)hexahydro-6*H*-furo[2,3-*b*]pyrrole-6-carboxylate (4k, Table 3, entry 10). Prepared following method D using **2k** (207 mg, 0.45 mmol), $NaCNBH_3$ (36 mg, 0.54 mmol), Bu_3SnH (6 μl, 0.02 mmol) and AIBN (7 mg, 0.04 mmol) to yield the bicyclic derivative which was purified by flash column chromatography (SiO_2, 30% EtOAc/70% hexane) affording a mixture of isomers *endo*/*exo* (80:20) **4k** (123 mg, 82%) as a colorless oil; R_f=0.32 (30% EtOAc/70% hexane); IR (film) ν 2978, 1737, 1713, 1497, 1455, 1414, 1356, 1259, 1101, 1122, 1092, 1042, 1006, 920, 773, 736, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers δ 7.34–7.24 (m, 5H, Ar), 5.73–5.68 (m, 1H, –NC*H*O), 5.27–5.04 (m, 2H, –CH_2-Ph), 4.10 (dq, J=7.7, 1.8 Hz, 2H, –OCH_2CH$_3$), 4.01 (t, J=7.9 Hz, 1H, –OCH_2), 3.57–3.40 (m, 3H, –OCH_2 and –NCH_2), 2.90–2.88 (m, 0.8H, C*H*CHCH$_2$), 2.72 (br, 0.8H, CHC*H*CH$_2$), 2.54 (br, 0.2H, C*H*CHCH$_3$), 2.41–2.30 (m, 2H, CHCH_2(C=O)), 2.05–1.20 (m, 0.2H, CHC*H*CH$_2$), 1.86–1.73 (m, 2H, –NCH$_2$CH_2), 1.22 (d, J=7.2 Hz, 3H, CH$_2$CH_3); ^1H NMR (400 MHz, d_2-tetrachloroethane, T=360 K) δ 7.40–7.34 (m, 5H, Ar), 5.90 (d, J=5.4 Hz, 1H, –NC*H*O), 5.25–5.20 (m, 2H, –CH_2Ph), 4.20 (q, J=7.1 Hz, 2H, –OCH_2CH$_3$), 4.05 (t, J=7.9 Hz, 1H, –OCH_2), 3.62–3.48 (m, 3H, –OCH_2 and –NCH_2), 2.96–2.92 (m, 0.8H, C*H*CHCH$_3$), 2.80–2.74 (m, 0.8H, CHC*H*CH$_3$), 2.57 (br, 0.2H, C*H*CHCH$_3$), 2.50–2.36 (m, 2H, CHCH_2(C=O)), 2.20–2.06 (m, 0.2H, CHC*H*CH$_3$), 1.90–1.81 (m, 2H, –NCH$_2$CH_2), 1.30 (d, J=7.1 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 171.8, 171.7, 154.8, 154.4, 136.5, 136.3, 128.4, 128.4, 128.32, 128.3, 128.2, 128.2, 128.1, 127.8, 92.8, 92.1, 91.4, 71.8, 70.5, 66.9, 60.6, 60.5, 48.7, 47.7, 47.1, 46.8, 45.7, 45.4, 44.4, 41.3, 37.6, 37.6, 32.0, 29.0, 28.4, 23.2, 22.6, 14.0; HRMS (EI) *m/z* calcd for ($C_{18}H_{23}NO_5^+$): 333.1576, found: 333.1590.

4.5.13. 6-*tert*-Butyl-5-methyl-(3a*R*,5*S*,6a*S*)-3-methylhexahydro-6*H*-furo[2,3-*b*]pyrrole-5,6-dicarboxylate (4m, Table 3, entry 11). Prepared following method D using **2m** (480 mg, 1.18 mmol), $NaCNBH_3$ (93 mg, 1.4 mmol), Bu_3SnH (16 μl, 0.06 mmol) and AIBN (20 mg, 0.12 mmol) to yield the bicyclic derivative **4m** which was purified by flash chromatography (SiO_2, 20% EtOAc/80% hexane) affording a mixture of the *endo*/*exo* isomers (95:5) (320 mg, 96%) as a colorless oil; R_f=0.35 (20% EtOAc/80% hexane); $[\alpha]_D^{20}$=+55.06 (c=0.77 g/100 ml in $CHCl_3$); IR (film) ν 2974, 2879, 1756, 1710, 1478, 1454, 1436, 1366, 1315, 1258, 1198, 1170, 1124, 1099, 1045, 1001, 930, 906, 882, 858, 798, 772, 733, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 5.70 (br, 1H, –NC*H*O–), 4.15–4.30 (m, 1H, –NC*H*CO$_2$CH$_3$), 3.87 (t, J=7.9 Hz, 1H, –OCH_2), 3.70 (s, 3H, –OCH_3), 3.50 (dd, J=11.0, 8.6 Hz, 1H, –OCH$_2$), 2.75 (br, 1H, –NCHC*H*), 2.38 (br, 1H, –CHC*H*CH$_3$), 2.13–2.05 (m, 1H, –NCHCH_2), 1.84–1.75 (m, 1H, –NCHCH_2), 1.44 (s, 4.5H, C(CH_3)$_3$), 1.37 (s, 4.5H, –C(CH_3)$_3$), 0.93 (d, J=7.0 Hz, 0.05H, –CHCH_3), 0.85 (d, J=6.8 Hz, 0.95H, CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 172.0, 171.6, 153.4, 93.6, 92.8, 80.8, 71.7, 60.7, 60.4, 52.0, 46.4, 45.5, 35.9, 28.2, 27.1, 18.7, 10.6; DEPT (100 MHz, $CDCl_3$), rotamers, δ 93.6(+), 71.7(−), 60.7(+), 60.4(+), 52.0(+), 46.4(+), 45.5(+), 35.9(+), 28.2(+), 27.1(−), 18.7(+), 10.6(+).

4.5.14. 6-*tert*-Butyl-5-methyl-(3a*S*,5*S*,6a*R*)-3-methylhexahydro-6*H*-furo[2,3-*b*]pyrrole-5,6-dicarboxylate (4m′, Table 3, entry 12). Prepared following method D using **2m′** (323 mg, 0.79 mmol), $NaCNBH_3$ (62 mg, 0.95 mmol), Bu_3SnH (11 μl, 0.04 mmol) and AIBN (13 mg, 0.08 mmol) to yield the bicyclic derivative **4m′** which was purified by flash chromatography (SiO_2, 40% EtOAc/60%hexane) affording a mixture of the isomers *endo*/*exo* (95:5) (170 mg, 76%) as a colorless oil; R_f=0.5 (40% EtOAc/60% hexane); $[\alpha]_D^{20}$=−113.33 (c=1.043 g/100 ml, $CHCl_3$); IR (film) ν 2973, 1748, 1704, 1478, 1456, 1436, 1391, 1365, 1312, 1257, 1204, 1169, 1134, 1091, 1050, 1023, 1004, 983, 930, 877, 857, 781, 666 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), rotamers, δ 5.61 (d, J=5.4 Hz, 0.5H, –NC*H*O–), 5.53 (d, J=5.3 Hz, 0.5H, –NC*H*O–), 4.23 (dd, J=19.5, 9.0 Hz, 1H, –NC*H*CO$_2$CH$_3$), 3.70 (t, J=7.7 Hz, 1H, –OCH_2), 3.52 (s, 3H, –OCH_3), 3.32–3.26 (m, 1H, –OCH_2), 2.68–2.62 (m, 1H, –NCHC*H*), 2.29–2.22 (m, 1H, –CHC*H*CH$_3$), 2.02–1.92 (m, 1H, –NCHCH_2), 1.68–1.63 (m, 1H, –NCHCH_2), 1.29 (s, 4.5H, –C(CH_3)$_3$), 0.77 (s, 4.5H, –C(CH_3)$_3$), 0.86 (d, J=6.9 Hz, 0.05H, –CHCH_3), 0.77 (d, J=6.8 Hz, 0.95H, CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 173.0, 172.7, 153.6, 93.4, 93.1, 80.5, 80.3, 71.5, 60.6, 60.3, 51.9, 51.8, 45.7, 4.6, 35.5, 28.1, 27.9, 27.4, 26.6, 10.20, 10.16; DEPT (100 MHz, $CDCl_3$), rotamers, δ 93.4(+), 93.1(+), 71.5(−), 60.6(+), 60.3(+), 51.9 (+), 51.8(+), 45.7(+), 4.6(+), 35.5(+), 28.1(+), 27.9(+), 27.4(−), 26.6(−), 10.2(+).

4.6. Method E. General procedure for aziridination/methanolysis

A solution of NaN(SiMe$_3$)$_2$ (1.1 mequiv) in THF was added dropwise to a stirred solution of the iodocarbamate **3** in dry THF and dry methanol (excess) at −78 °C and under nitrogen. The mixture was stirred for 5 min at −78 °C and then allowed to reach rt. A saturated aqueous solution of $NaHCO_3$ and diethyl ether were added, the organic layer separated and the aqueous layer extracted with diethyl ether. The combined organic phases were dried (Na_2SO_4) and the solvent removed in vacuo to yield the 3-carbamoyl-2-methoxy derivative **5**, which was purified by flash chromatography.

4.6.1. Benzyl-3-[*tert*-butoxycarbonyl)amino]-2-methoxy-1-pyrrolidinecarboxylate (5a, Table 4, entry 1). Prepared following method E using **3a** (298 mg, 0.67 mmol) and NaN(SiMe$_3$)$_2$ (0.5 M in toluene, 1.46 ml, 0.73 mmol) to yield the crude product which was purified by flash chromatography (SiO_2, 30% EtOAc/70% hexane) affording a *cis*/*trans* mixture (15:85) of **5a** (184 mg, 82%) as a yellow oil; R_f=0.3 (20% EtOAc/80% hexane); IR (filme) ν 3336, 2976, 1711, 1518, 1453, 1410, 1365, 1285, 1247, 1169, 1116, 1078, 1048, 1020, 973, 915, 881, 750, 698, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.32–7.23 (m, 5H, Ar), 5.19–5.07 (m, 2H, –CH_2Ph), 5.02 (s, 0.5H, –NC*H*O), 4.95 (s, 0.5H, –NC*H*O), 4.85 (br, 1H, –N*H*), 4.10 (br, 0.3H, –C*H*NHBoc), 3.98 (br, 0.7H, –C*H*NHBoc), 3.51–3.30 (m, 5H, –NCH_2 and –OCH_3), 2.28 (br, 1H, –NCH$_2$CH_2), 1.76 (br, 1H, –NCH$_2$CH_2), 1.41 (br, 9H, –C(CH_3)$_3$); ^{13}C NMR

(100 MHz, $CDCl_3$), rotamers, δ 155.0, 136.3, 133.1, 130.9, 128.5, 128.1, 127.9, 93.0, 92.4, 67.2, 56.4, 55.9, 55.2, 54.4, 43.9, 43.7, 28.3, 28.2, 27.5, 18.5; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.5(+), 128.1(+), 127.9(+), 93.0(+), 92.4(+), 67.2(−), 56.4(+), 55.9(+), 55.2(+), 54.4(+), 43.9(−), 43.7(−), 28.3(+), 28.2(+), 27.5(−).

4.6.2. Benzyl-3-[(benzyloxycarbonyl)amino]-2-methoxy-1-pyrrolidinecarboxylate (5b, Table 4, entry 2). Prepared following method E using **3b** (298 mg, 0.62 mmol) and $NaN(SiMe3)_2$ (0.5 M in toluene, 1.49 ml, 0.74 mmol) to yield the crude product which was purified by flash column chromatography (SiO_2, 30% EtOAc/70% hexane) affording a *cis*/*trans* mixture (23:77) of **5b** (173 mg, 73%) as a yellow oil; R_f=0.38 (30% EtOAc/70% hexane); IR (film) ν 3323, 3032, 2952, 1704, 1531, 1454, 1408, 1338, 1295, 1240, 1112, 1240, 1078, 968, 912, 773, 739, 697, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.26–7.20 (m, 5H, Ar), 5.24–4.94 (m, 5.5H, –NC*H*O–, N*H* and 2×(–CH_2Ph)), 4.59 (s, 0.5H, –N*H*), 4.01 (br, 0.8H, –C*H*NHCbz), 3.89 (br, 0.2H, –C*H*NHCbz), 3.44–3.23 (m, 5H, –NCH_2CH_2 and –OCH_3), 2.26–2.16 (m, 1H, –NCH$_2$CH_2), 1.74–1.71 (m, 1H, –NCH$_2$CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.9, 155.8, 155.2, 154.9, 141.3, 136.3, 128.5, 128.4, 128.2, 128.1, 127.9, 127.6, 127.4, 126.9, 92.9, 92.4, 86.8, 86.3, 67.5, 67.3, 67.2, 66.9, 64.9, 57.2, 56.6, 56.3, 55.8, 55.7, 55.1, 53.2, 52.5, 44.1, 43.8, 43.4, 28.5, 28.3, 27.3; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.5(+), 128.4(+), 128.2(+), 128.1(+), 127.9(+), 127.4(+), 126.9(+), 92.9(+), 92.4(+), 86.8(+), 86.3(+), 67.5(−), 67.3(−), 67.2(−), 66.9(−), 57.2(+), 56.6(+), 56.3(+), 55.8(+), 55.7(+), 55.1(+), 53.2(+), 52.5(+), 44.1(−), 43.8(−), 43.4(−), 28.5(−), 28.3(−), 27.3(−).

4.6.3. Benzyl-2-methoxy-3-[(methoxycarbonyl)amino]-1-pyrrolidinecarboxylate (5c, Table 4, entry 3). Prepared following method E using **3c** (4.76 g, 11.8 mmol) and $NaN(SiMe_3)_2$ (0.5 M in toluene, 25.9 ml, 12.9 mmol) to yield the crude product which was purified by flash column chromatography (SiO_2, 40% EtOAc/60% hexane) affording a *cis*/*trans* mixture (22:77) of **5c** (3.1 g, 85%). as a yellow oil; R_f=0.23 (30% EtOAc/70% hexane); IR (film) ν 3321, 2954, 1683, 1694, 1699, 1713, 1538, 1455, 1418, 1348, 1246, 1082, 974, 773, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.31–7.26 (m, 5H, Ar), 5.45 (d, J= 5.2 Hz, 0.78H, –NC*H*O–), 5.35 (br, 0.22H, –NC*H*O–), 5.19–4.95 (m, 3H, –CH_2Ph and –N*H*), 4.01 (br, 0.78H, –C*H*NH(CO$_2$Me)), 3.86 (br, 0.22H, –C*H*NH(CO$_2$Me)), 3.66–3.29 (m, 4H, 1×–NCH_2CH$_2$ and –OCH_3), 2.29 (br, 1H, –NCH_2CH$_2$), 1.76 (br, 1H, –NCH$_2$CH_2), 1.83–1.74 (m, 1H, –NCH$_2$CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 156.6, 156.0, 155.4, 136.5, 128.7, 128.3, 128.1, 93.1, 92.6, 67.5, 67.4, 56.5, 56.0, 55.8, 55.2, 52.4, 44.2, 44.0, 28.6, 27.6.

4.7. Method F. General procedure for azidomethoxylation

CAN (3 mequiv) dissolved in acetonitrile was added dropwise to a cooled (ice-bath) mixture of sodium azide (1.5 mequiv) and the enecarbamate (1 mequiv), in dry acetonitrile and dry methanol and under nitrogen. The mixture was gradually brought to rt and stirred overnight. Water and diethyl ether were added and the organic layers separated and washed with ice-cold water. The aqueous layer was extracted once again with diethyl ether, the combined organic layers dried (Na_2SO_4) and the solvent removed in vacuo. Purification by column chromatography afforded the 3-azido-2-methoxy derivative **6**.

4.7.1. Benzyl-3-azido 2-methoxy-1-pyrrolidinecarboxylate (6a, Scheme 1). Prepared following method F using **1a** (1.0 g, 4.93 mmol), sodium azide (480 mg, 7.4 mmol), and CAN (5.4 g, 9.8 mmol) to yield the crude product which was purified by flash chromatography (SiO_2, 10% EtOAc/90% hexane), affording a mixture of *cis*/*trans*-**6a** (30/70) (372 mg, 27%) as a colorless oil; R_f=0.44 (20% EtOAc/80% hexane); IR (film) ν 3033, 2954, 2835, 2105, 1716, 1694, 1699, 1641, 1498, 1455, 1418, 1337.5, 1176, 1115, 1029, 985, 931, 772, 753, 698, 605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.36–7.29 (m, 5H, Ar), 5.25–4.89 (m, 3H, –CH_2Ph and –NC*H*O–), 3.93 (d, J= 6.4 Hz, 0.7H, –C*H*N$_3$), 3.54–3.42 (m, 5.3H, –OCH_3, 0.3×–C*H*N$_3$ and –NCH_2), 2.31–2.24 (m, 1H, –NCH$_2$CH_2), 2.20–1.96 (m, 1H, –NCH$_2$CH_2); ^1H NMR (300 MHz, d_2-tetrachloroethane, T=365 K), rotamers, δ 7.40–7.35 (m, 5H, Ar), 5.24–5.19 (m, 2.7H, –CH_2Ph and 0.7×–NC*H*O–), 5.08 (br, 0.3H, –NC*H*O–), 3.97 (d, J=5.1 Hz, 0.7H, –C*H*N$_3$), 3.63–3.39 (m, 5.3H, –OCH_3, 0.3×–C*H*N$_3$ and –NCH_2), 2.36–2.00 (m, 2H, NCH$_2$CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 156.0, 136.6, 128.8, 128.7, 128.4, 128.3, 128.2, 128.0, 92.2, 91.6, 88.5, 88.2, 67.6, 67.4, 64.8, 64.2, 60.8, 60.2, 57.4, 56.9, 56.5, 55.9, 44.4, 44.2, 43.3, 43.2, 28.2, 27.3, 26.3, 25.3; HRMS (EI) *m*/*z* calcd for ($C_{13}H_{16}N_4O_3^+$) requires: 275.1144, found: 275.1108.

4.7.2. Benzyl-3-azido-2-methoxy-1-piperidinecarboxylate (6b, Scheme 1). Prepared following method F using **1d** (0.76 g, 3.5 mmol), sodium azide (0.34 g, 5.25 mmol) and CAN (5.82 g, 10.5 mmol) to yield the crude product which was purified by flash column chromatography (SiO_2, 40% EtOAc/60% hexane) affording a mixture of *cis*/*trans*-**6b** (40/60) (0.69 g, 71%) as a colorless oil; R_f=0.65 (20% EtOAc/80% hexane); IR (film) ν 3032, 2946, 2103, 1699, 1498, 1418, 1345, 1307, 1263, 1162, 1121, 1079, 1039, 965 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.37–7.26 (m, 5H, Ar), 5.5 (br, 0.6H, –NC*H*–O), 5.36 (br, 0.4H, –NC*H*O–), 5.24–5.08 (m, 2H, –CH_2Ph), 3.96–3.87 (m, 1H, –NCH_2), 3.76 (br, 0.4H, –C*H*N$_3$), 3.35–2.91 (m, 4.6H, –OCH_3, 0.6×–C*H*N$_3$ and 1×–NCH_2), 2.03–1.43 (m, 4H, –NCH$_2$(CH_2)$_2$);^1H NMR (300 MHz, d_2-tetrachloroethane, T=350 K), rotamers, δ 7.43–7.39 (m, 5H, Ar), 5.46 (br, 0.6H, –NC*H*O–), 5.31 (br, 0.4H, –NC*H*O–), 5.23–5.20 (m, 2H, –CH_2Ph), 4.03–3.93 (m, 1H, –NCH_2), 3.77 (br, 0.4H, –C*H*N$_3$), 3.37 (s, 1.8H, –OCH_3), 3.30 (s, 1.2H, –OCH_3), 3.15 (d, J=12.3 Hz, 0.6H, –C*H*N$_3$), 3.02–2.94 (m, 1H, NCH_2), 2.05–1.51 (m, 4H, NCH$_2$(CH_2)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.8, 155.2, 128.8, 128.7, 128.6, 128.4, 128.3, 128.1, 84.1, 83.8, 83.1, 67.8, 67.9, 59.2, 59.1, 58.2, 55.6, 55.2, 38.0, 37.6, 24.5, 24.2, 23.5, 23.3, 23.2, 19.6.

4.8. Method G. General procedure for $LiAlH_4$ reduction

To a stirred suspension of $LiAlH_4$ (5 mequiv) in dry THF at

0 °C and under nitrogen was slowly added a solution of the bicyclic compound **4** (1 mequiv) in THF. After refluxing for 14 h, the mixture was cooled to rt and carefully treated with H_2O, aqueous NaOH (15%), and again with H_2O. The white precipitate was filtered and washed several times with Et_2O. After acidification with aqueous H_2SO_4 (10%), the ethereal phase was separated, the aqueous layer basified (pH=14) and extracted with dichloromethane. Removal of the solvent in vacuo afforded the *N*-alkyl-3-alkyl-pyrrolidine derivative **7**.

4.8.1. 2-(1-Methyl-3-pyrrolidinyl)-2-propen-1-ol (7a, Scheme 2). Prepared following method G using **4a** (128 mg, 0.49 mmol) and $LiAlH_4$ (93 mg, 2.45 mmol) to yield the **7a** (43.6 mg, 62%) as a colorless oil; IR (film) ν 3367 (O–H), 2945, 2789, 1648, 1450, 1349, 1233, 1151, 1081, 1037, 894, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.84–4.83 (m, 1H, C=CH_2), 4.78 (m, 1H, –C=CH_2), 4.18–4.14 (dd, J=13.6, 1.2 Hz, 1H, –CH_2=CCH_2OH), 4.00–3.96 (dd, J=13.6, 1.2 Hz, 1H, –CH_2=CCH_2OH), 3.01–2.96 (m, 1H, –NCH_2CH_2), 2.93 (dt, J=8.8, 3.6 Hz, 1H, –NCH_2CH), 2.72 (dd, J=9.6, 2.8 Hz, 1H, –NCH_2CH), 2.48–2.31 (m, 1H, –NCH_2CH), 2.32 (s, 3H, N–CH_3), 2.24–2.14 (m, 1H, NCH_2CH), 2.10–2.01 (m, 1H, –NCH_2CH_2), 1.85–1.39 (m, 1H, –NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 111.5, 64.3, 61.8, 55.5, 43.3, 41.2, 29.2; HRMS (EI) m/z calcd for ($C_8H_{15}NO^+$): 141.1154, found: 141.1151.

4.8.2. 2-(1-Ethyl-3-pyrrolidinyl)-2-propen-1-ol (7b, Scheme 2). Prepared following method G using **4e** (117 mg, 0.7 mmol) and $LiAlH_4$ (133 mg, 3.5 mmol) to yield **7b** (63.3 mg, 58%) as a colorless oil; IR (film) ν 3359, 2960, 2927, 2808, 1652, 1483, 1455, 1390, 1346, 1216, 1158, 1106, 1042, 896 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.82 (s, 1H, –C=CH_2), 4.7 (d, J=1.4 Hz, 1H, –C=CH_2), 4.15–4.12 (dd, J=13.2, 0.7 Hz, 1H, CH_2=CCH_2–OH), 3.95 (d, J=13.2 Hz, 1H, CH_2=CCH_2–OH), 2.98–2.92 (m, 2H, –NCH_2CH_2 and –NCH_2CH), 2.76 (dd, 1H, J=9.5, 2.6 Hz, –NCH_2CH_2), 2.31 (q, J=7.2 Hz, 2H, –NCH_2CH_3), 2.28–2.25 (m, 1H, –NCH_2CH_3), 2.23–2.16 (m, 1H, –CHC=CH_2), 2.14–2.00 (m, 1H, –NCH_2CH_2), 1.79–1.76 (m, 1H, –NCH_2CH_2), 1.06 (t, J=7.3 Hz, 3H, –NCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 111.4, 64.2, 59.3, 53.0, 49.2, 42.6, 28.4, 13.6; HRMS (EI) m/z calcd for ($C_9H_{17}NO^+$): 155.1310, found: 155.1308.

4.9. Method H. General procedure for nucleophilic substitution of 4 via *N*-acyl-iminium formation

To a stirred solution of the bicyclic compound (1 quiv) and the nucleophile (5 quiv) in dry dichloromethane at 0 °C was added BF_3.OEt_2 (4 quiv). The resulting mixture was stirred at rt (1 h for the *N*-Cbz-bicyclic substrate and 2 days for the *N*-acetyl-bicyclic substrate). Na_2CO_3 (sat. aq. soln) was then added, the phases were separated and the aqueous phase extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and the solvent removed in vacuo to yield the 2,3-dialkylsubstituted pyrrolidine derivative **8**, which was purified by flash chromatography.

4.9.1. Benzyl-2-allyl-3-[1-hydroxymethy)vinyl]-1-pyrrolidinecarboxylate (8a, Table 5, entry 1). Prepared following method H using **4a** (453 mg, 1.75 mmol), allyltrimethylsilane (1.39 ml, 8.75 mmol) and $BF_3 \cdot OEt_2$ (0.887 ml, 7.0 mmol) to yield the 2,3-dialkylsubstituted pyrrolidine derivative which was purified flash column chromatography (SiO_2, 40% EtOAc/60% hexane) affording a mixture of *cis*/*trans*-**8a** (76/24) (450 mg, 89%) as a colorless oil; R_f=0.18 (30% EtOAc/70% hexane); IR (film) ν 3431, 3074, 2952, 1685, 1420, 1357, 1185, 1113, 913, 767, 735, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers δ 7.34–7.24 (m, 5H, Ar), 5.86–5.64 (m, 1H, –CH_2CH=CH_2), 5.29–4.93 (m, 5H, –CH_2Ph and 3×(–C=CH_2)$_2$), 4.85 (d, J=12.8 Hz, 1H, 1×–C=CH_2), 4.18–4.15 (m, 0.4H, –NCHCH), 4.06 (s, 2H, –CH_2OH), 3.93–3.85 (m, 0.6H, –NCHCH), 3.77–3.28 (m, 2H, –NCH_2CH_2), 2.79–2.76 (m, 0.4H, –NCHCH), 2.64 (br, 0.8H, CH_2CH=CH_2), 2.47–2.39 (m, 0.6H, –NCHCH), 2.36–1.79 (m, 2.2H, 1.2×CH_2-CH=CH_2 and 1×–NCH_2CH_2), 1.78–1.72 (m, 1H, –NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 154.5, 154.3, 149.0, 149.0, 145.4, 145.3, 136.5, 136.4, 136.2, 136.1, 135.2, 135.2, 134.0, 133.8, 128.0, 128.0, 127.8, 127.6, 127.6, 127.5, 127.4, 127.21, 117.5, 117.5, 116.4, 111.0, 110.7, 108.9, 66.6, 66.2, 65.3, 65.2, 64.3, 61.0, 60.6, 57.7, 57.4, 45.6, 45.3, 44.4, 44.3, 43.6, 38.0, 37.0, 35.0, 34.7, 28.8, 28.0, 25.8, 24.9; HRMS (EI) m/z calcd for ($C_{18}H_{23}NO_3+H^+$): 302.1756, found: 302.1748.

4.9.2. 2-(1-Acetyl-2-allyl-3-pyrrolidinyl)-2-propen-1-ol (8b, Table 5, entry 2). Prepared following method H using **4e** (205 mg, 1.23 mmol), allyltrimethylsilane (0.98 ml, 6.15 mmol) and $BF_3 \cdot OEt_2$ (0.623 ml, 4.92 mmol) to yield a mixture of the *cis*/*trans*-2,3-dialkylsubstituted pyrrolidine derivative which was purified by flash chromatography (SiO_2, 80% EtOAc/20% hexane) affording the *cis*-**8b** and *trans*-**8b**(combined yield 58%).

4.9.3. *trans*-2-(1-Acetyl-2-allyl-3-pyrrolidinyl)-2-propen-1-ol (*trans*-8b). (56 mg, 21%) as a yellow oil; R_f=0.43 (EtOAc); IR (film) ν 3392, 3077, 2926, 1620, 1446, 1430, 1358, 1036, 912 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 5.65–5.56 (m, 1H, –CH_2CH=CH_2), 5.13–4.94 (m, 2.8H, –C=CH_2), 4.73 (s, 0.9H, –C=CH_2), 4.67 (s, 0.3H, –C=CH_2), 4.15 (dt, J=8.5, 3.5 Hz, 0.67H, –NCHCH), 4.07 (s, 2H, –CH_2OH), 3.80 (ddd, J=8.8, 4.0, 1.7 Hz, 0.33H, N–CHCH), 3.69–3.61 (m, 0.32H, –NCH_2CH_2), 3.52–3.36 (m, 1.68H, N–CH_2CH_2), 2.72–2.71 (m, 0.35H, –NCHCH), 2.66 (dt, J=7.0, 4.0 Hz, 0.65H, –NCHCH), 2.53–2.46 (m, 0.84H, –CH_2CH=CH_2), 2.38–1.78 (m, 3.16H, 1.16×–CH_2CH=CH_2 and –NCH_2CH_2), 2.08 (s, 0.78H, –CH_3), 2.02 (s, 2.22H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 169.2, 149.8, 149.2, 145.4, 134.3, 133.4, 118.4, 118.0, 117.5, 116.6, 111.7, 109.0, 67.9, 64.7, 64.6, 64.4, 62.6, 60.4, 50.2, 46.8, 46.3, 45.5, 45.1, 44.6, 44.5, 43.2, 39.4, 36.9, 29.6, 28.9, 27.8, 27.1, 22.6, 21.9; DEPT (100 MHz, $CDCl_3$), rotamers, δ 134.3(+), 133.4(+), 118.4(−), 118.0(−), 117.5(−), 116.6(−), 111.7(−), 109.0(−), 64.6(−), 64.4(−), 62.6(+), 60.4(+), 50.2(+), 46.8(−), 46.3(−), 45.5(+), 45.1(+), 44.6(+), 44.5(+), 43.2(+), 39.4(−), 36.9(−), 29.6(−), 28.9(−), 27.8(−), 27.1(−), 22.6(+), 21.9(+); HRMS (EI) m/z calcd for ($C_{12}H_{19}NO_2+H^+$): 210.1494, found: 210.1483.

4.9.4. *cis*-2-(1-Acetyl-2-allyl-3-pyrrolidinyl)-2-propen-1-ol (*cis*-8b). (94 mg, 37%) as a yellow oil; R_f=0.26 (EtOAc); IR (film) ν 3390, 3077, 2932, 2887, 1619, 1445,

1429, 1352, 1184, 1067, 1040, 999, 908 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 5.83–5.66 (m, 1H, $-CH_2CH{=}CH_2$), 5.27–4.25 (m, 1H, $-C{=}CH_2$), 5.04–4.90 (m, 3H, $-C{=}CH_2$), 4.34 (q, $J=6.5$ Hz, 0.68H, –NCHCH), 4.18–4.06 (m, 2H, $-CH_2OH$), 4.01 (q, $J=6.5$ Hz, 0.32H, –NCHCH), 3.57–3.65 (m, 2H, $-NCH_2CH_2$), 2.90 (dt, $J=$ 13.2, 7.5 Hz, 0.32H, –NCHCH), 2.75 (dt, $J=13.0$, 7.5 Hz, 0.68H, –NCHCH), 2.28–1.84 (m, 4H, $-CH_2CH{=}CH_2$ and $-NCH_2CH_2$), 2.07 (s, 0.94H, $-CH_3$), 2.01 (s, 2.06H, $-CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 169.5, 145.6, 135.6, 134.6, 118.0, 117.4, 116.3, 112.0, 111.0, 65.7, 65.3, 59.4, 56.8, 46.0, 45.4, 45.3, 43.6, 43.4, 34.9, 34.2, 26.2, 25.8, 24.4, 22.4, 22.1; DEPT (100 MHz, $CDCl_3$) δ 135.6(+), 134.6(+), 118.0(−), 117.4(−), 116.3(−),112.0(−), 111.0(−), 65.7(−), 65.3(−), 59.4(+), 56.8(+), 46.0(−), 45.4(+), 45.3(−), 43.6(+), 43.4(+), 34.9(−), 34.2(−), 26.2(−), 25.8(−), 24.4(−), 22.4(+), 22.1(+); HRMS (EI) m/z calcd for ($C_{12}H_{19}NO_2+H^+$): 210.1494, found: 210.1489

4.9.5. Benzyl-2-cyano-3-[1-hydroxymethyl)vinyl]-1-pyrrolidinecarboxylate (8c, Table 5, entry 3). Prepared following method H using **4a** (150 mg, 0.58 mmol), cyanotrimethylsilane (386 µl, 2.9 mmol) and $BF_3{\cdot}OEt_2$ (293 µl, 2.32 mmol) to yield the 2,3-dialkyl-substituted pyrrolidine derivative which was purified by flash column chromatography (SiO_2, 60% EtOAc/40% hexane) affording a mixture of *cis*/*trans*-**8c** (67:33) (125 mg, 76%) as a colorless oil; $R_f=0.32$ (50% EtOAc/50% hexane); IR (film) ν 3440, 2950, 2891, 1705, 1494, 1416, 1357, 1214, 1190, 1126, 1057, 1028, 915, 763, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.39–7.31 (m, 5H, Ar), 5.34 (s, 1H, $-C{=}CH_2$), 5.27–5.13 (m, 3H, $1\times-C{=}CH_2$ and CH_2Ph), 4.99–4.89 (m, 0.67H, –NCHCN), 4.57–4.49 (m, 0.33H, –NCHCN), 4.19–4.10 (m, 2H, $-CH_2OH$), 3.72–3.36 (m, 1H, $-NCH_2CH_2$), 3.52–3.50 (m, 0.33H, $-NCH_2CH_2$), 3.43–3.35 (m, 0.67H, $-NCH_2CH_2$), 3.26–3.22 (m, 0.33H, $-CHC{=}CH_2$), 3.09–3.04 (m, 0.67H, $-CHC{=}CH_2$), 2.27–2.10 (m, 2H, $-NCH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 153.6, 145.1, 135.8, 128.5, 128.2, 128.1, 128.0, 118.8, 118.4, 116.8, 116.7, 115.2, 114.8, 112.8, 112.6, 68.6, 68.0, 67.8, 67.7, 67.6, 66.6, 66.4, 65.0, 52.2, 51.8, 51.6, 51.2, 47.5, 46.4, 45.8, 45.4, 45.2, 45.1, 45.0, 44.2, 29.6, 28.8, 27.6, 26.7; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.5(+), 128.2(+), 128.1(+), 128.0(+), 118.8(−), 118.4(−), 116.8(−), 116.7(−), 115.2(−), 114.8(−), 112.8(−), 112.6(−), 68.6(−), 68.0(−), 67.8(−), 67.7(−), 67.6(−), 66.6(−), 66.4(−), 65.0(−), 52.2(+), 51.8(+), 51.6(+), 51.2(+), 47.5(+), 46.4(+), 45.8(−), 45.4(−), 45.2(−), 45.1(−), 45.0(−), 44.2(+), 29.6(−), 28.8(−), 27.6(−), 26.7(−); HRMS (EI) m/z calcd for ($C_{16}H_{18}N_2O_3^+$): 286.1317, found: 286.1330.

4.9.6. 1-Acetyl-3-[1-(hydroxymethyl)vinyl]-2-pyrrolidinecarbonitrile (8d, Table 5, entry 4). Prepared following method H using **4e** (160 mg, 0.96 mmol), cyanotrimethylsilane (638 µl, 4.8 mmol) and $BF_3{\cdot}OEt_2$ (486 µl, 3.84 mmol) to yield the 2,3-dialkylsubstituted pyrrolidine derivative which was purified by flash column chromatography (SiO_2, 90%EtOAc/10% hexane) affording a mixture of *cis*/*trans*-**8d** (74:26) (120 mg, 64%) as a colorless oil; $R_f=0.26$ (EtOAc); IR (film) ν 3390, 2947, 2892, 1644, 1651, 1417, 1359, 1300, 1260, 1184, 1037, 917, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 5.38 (br, 1H, $C{=}CH_2$), 5.21–5.13 (m, 1.74H, $C{=}CH_2$ and –NCHCN), 4.92 (d, $J=7.1$ Hz, 0.26H, –NCHCN), 4.28–4.16 (m, 2H, $-CH_2OH$), 3.79–3.70 (m, 1H, $-NCH_2CH_2$), 3.53–3.39 (m, 1H, $-NCH_2CH_2$), 3.17–3.13 (m, 0.26H, $-CHC{=}CH_2$), 3.10–3.04 (m, 0.74H, $-CHC{=}CH_2$), 2.38–2.33 (m, 1H, $-NCH_2CH_2$), 2.26–2.19 (m, 1H, $-NCH_2CH_2$), 2.22 (s, 0.5H, $-CH_3$), 2.09 (s, 2.5H, $-CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 169.5, 143.4, 143.1, 116.2, 115.8, 114.6, 114.0, 66.1, 65.6, 52.5, 50.3, 45.9, 45.0, 44.5, 27.8, 26.1, 22.3, 21.6; DEPT (100 MHz, $CDCl_3$), rotamers, δ 115.7(+), 114.8(+), 67.0(+), 66.3(+), 52.5(−), 50.3(−), 46.1(+), 45.0(−), 44.7(+), 44.5(−), 29.6(+), 28.1(+), 26.3(+), 22.3(−), 21.6(−); HRMS (EI) m/z calcd for ($C_{10}H_{14}N_2O_2^+$): 194.1055, found: 194.1053.

4.9.7. Benzyl-2-allyl-3[(benzyloxycarbonyl)amino]-1-pyrrolidinecarboxylate (9a, Table 6, entry 1). Prepared following method H using **5b** (55 mg, 0.14 mmol), allyltrimethylsilane (46 µl, 0.28 mmol, 2 quiv) and $BF_3{\cdot}OEt_2$ (36 µl, 0.28 mmol, 2 quiv) to yield the substituted pyrrolidine which was purified by preparative thin layer chromatography (SiO_2, 40%EtOAc/60% hexane) affording the *cis* (24%) and *trans* (76%) isomers of **9a** (35 mg, 60%) as colorless oils.

4.9.8. *trans*-Benzyl-2-allyl-3-[(benzyloxycarbonyl)-amino]-1-pyrrolidinecarboxylate (*trans*-9a). $R_f=0.37$ (30% AcOE/70% hexane); IR (film) ν 3313, 3064, 3032, 2952, 1698, 1586, 1532, 1498, 1454, 1415, 1349, 1278, 1244, 1114, 1028, 1002, 916, 846, 769, 697, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers δ 7.27–7.16 (m, 5H, Ar), 5.70 (br, 1H, $-CH_2CH{=}CH_2$), 5.13–4.93 (m, 7H, N*H*, $2\times(-CH_2Ph)$ and $-C{=}CH_2$), 4.29 (br, 1H, –NH), 4.00 (br, 1H, –CHNH), 3.74 (br, 1H, –NCHCH), 3.47–3.32 (m, 2H, $-NCH_2CH_2$), 2.46 (br, 0.5H, $-CH_2CH{=}CH_2$), 2.33 (br, 0.5H, $-CH_2CH{=}CH_2$), 2.13–2.11 (br, 2H, $-CH_2CH{=}CH_2$ and $-NCH_2CH_2$), 1.77 (br, 1H, $-NCH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.6, 136.2, 133.6, 128.5, 128.2, 128.0, 127.9, 118.2, 67.0, 66.8, 63.6, 54.9, 54.0, 44.4, 44.1, 37.7, 36.8, 29.9, 29.0; DEPT (100 MHz, $CDCl_3$), rotamers, δ 133.6(+), 128.5(+), 128.2(+), 128.0(+), 127.9(+), 118.2(−), 67.0(−), 66.8(−), 63.6(+), 54.9(+), 54.0(+), 44.4(−), 44.1(−), 37.7(−), 36.8(−), 29.9 (−), 29.0(−).

4.9.9. *cis*-Benzyl-2-allyl-3-[(benzyloxycarbonyl)amino]-1-pyrrolidinecarboxylate (*cis*-9a). $R_f=0.26$ (30% EtOAc/70% hexane); IR (film) ν 3304, 3065, 3031, 2915, 1693, 1538, 1452, 1412, 1358, 1239, 1113, 1026, 916, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.28–7.19 (m, 5H, Ar), 5.70 (br, 1H, $-CH_2CH{=}CH_2$), 5.09–4.84 (m, 7H, N*H*, $2\times(-CH_2Ph)$ and $-CH{=}CH_2$), 4.24 (br, 1H, $-CH_2CHNH$), 4.15–4.12 (m, 1H, –NCHCH–), 3.40 (dt, $J=$ 8.8, 2.0 Hz, 2H, $-NCH_2CH_2$), 2.20 (br, 3H, $-CH_2CH{=}CH_2$ and $-NCH_2CH_2$), 1.74–1.69 (m, 1H, $-NCH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.7, 155.1, 135.1, 128.6, 128.5, 128.3, 128.2, 128.0, 117.3, 77.2, 67.0, 56.8, 52.5, 43.4, 34.3, 29.7; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.6(+), 128.5(+), 128.3(+), 128.2(+), 128.0(+), 117.3(−), 77.2(+), 67.0(−), 56.8(+), 52.5(+), 43.4(−),

34.3(−), 29.7(−); HRMS (EI) *m/z* calcd for ($C_{23}H_{26}N_2O_4+H^+$): 395.1970, found: 395.1971.

4.9.10. Benzyl-3-[(benzyloxycarbonyl)amino]-2-cyano-1-pyrrolidinecarboxylate (9b, Table 6, entry 2). Prepared following method H using **5b** (89 mg, 0.23 mmol), cyanotrimethylsilane (63 μl, 0.46 mmol, 2 quiv) and $BF_3\cdot OEt_2$ (58 μl, 0.46 mmol, 2 quiv) to yield the substituted pyrrolidine which was purified by flash chromatography (SiO_2, 40%EtOAc/60% hexane) affording the *cis* (30%) and *trans* (70%) isomers of **9b** (44.8 mg, 52%) as colorless oils.

4.9.11. *trans*-Benzyl-3-[(benzyloxycarbonyl)amino]-2-cyano-1-pyrrolidinecarboxylate (*trans*-9b). R_f=0.29 (30% EtOAc/70%hexane); IR (film) ν 3307, 3071, 3031, 2956, 1710, 1536, 1454, 1413, 1358, 1284, 1244, 1218, 1172, 1133, 1027, 913, 738, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.36–7.19 (m, 5H, Ar), 5.36–5.30 (m, 1H, –NC*H*CN), 5.21–5.05 (m, 4H, 2×(–CH_2Ph)), 4.63–4.57 (m, 1H, –N*H*), 4.47 (br, 1H, –CH_2C*H*NH), 3.61–3.20 (m, 2H, –NC$H_2$$CH_2$), 1.27–1.79 (m, 2H, –NC$H_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.4, 155.3, 135.7, 128.6, 128.5, 128.4, 128.2, 128.0, 116.9, 76.7, 68.0, 67.9, 66.3, 58.9, 56.3, 55.3, 53.1, 44.5, 44.1, 30.3, 29.2, 18.6; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.6(+), 128.5(+), 128.4(+), 128.2(+), 128.0(+), 76.7(−), 68.0(−), 67.9(−), 66.3(−), 58.9(+), 56.3(+), 55.3(+), 53.1(+), 44.5(−), 44.1(−), 30.3(−), 29.2(−),18.6(−).

4.9.12. *cis*-Benzyl-3-[(benzyloxycarbonyl)amino]-2-cyano-1-pyrrolidinecarboxylate (*cis*-9b). R_f=0.22 (30% EtOAc/70% hexane); IR (film) ν 3321, 3033, 2957, 1711, 1532, 1454, 1413, 1357, 1284, 1241, 1177, 1114, 1040, 980, 913, 738, 698, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.28–7.19 (m, 5H, Ar), 5.23–5.19 (m, 1H, –NC*H*CN), 5.15–5.05 (m, 4H, 2×(–CH_2Ph)), 4.85 (br, 1H, –N*H*), 4.34 (br, 1H, –CH_2C*H*NH), 3.59–3.57 (m, 1H, –NC$H_2$$CH_2$), 3.35–3.32 (m, 1H, –NC$H_2$$CH_2$), 2.25–2.20 (m, 1H, –NC$H_2CH_2$), 1.93–1.91 (m, 1H, NC$H_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.6, 153.6, 135.7, 128.6, 128.4, 128.2, 115.9, 68.1, 67.9, 67.5, 53.4, 52.5, 52.3, 51.5, 51.3, 43.8, 29.6, 28.5.

4.9.13. Benzyl-3-[(benzyloxycarbonyl)amino]-2-(ethoxy-2-oxoethyl)-1-pyrrolidinecarboxylate (9c, Table 6, entry 3). Prepared following method H using **5b** (58 mg, 0.15 mmol), *tert*-butyl[1-ethoxyvinyl)oxy]dimethylsilane (202 mg, 0.6 mmol, 4 quiv) and $BF_3\cdot OEt_2$ (38 μl, 0.30 mmol, 2 quiv) to yield the 2,3-disubstituted pyrrolidine which was purified by flash chromatography (SiO_2, 40% EtOAc/60% hexane) affording a *cis*/*trans*-**9c** mixture (15/85) (49 mg, 74%) as a colorless oil; R_f=0.56 (40% EtOAc/60% hexane); IR (film) ν 3322, 3032, 2980, 2897, 1703, 1586, 1532, 1498, 1454, 1416, 1350, 1288, 1241, 1204, 1116, 1057, 1028, 978, 915, 770, 739 cm^{-1}; ^1H NMR (400 MHz, d_2-tetrachloroethane, T=340 K) δ 7.41–7.34 (m, 5H, Ar), 5.17 (s, 2H, –CH_2Ph), 5.14 (s, 2H, –CH_2Ph), 4.98 (d, J=5.0 Hz, 1H, –N*H*), 4.32–4.07 (m, 4H, –C*H*NH, NC*H*CH_2, –OC$H_2$$CH_3$), 3.65–3.59 (m, 1H, –NC$H_2$$CH_2$), 3.53–3.47 (m, 1H, –NC$H_2$$CH_2$), 2.88–2.84 (m, 1H, –$CH_2$(C=O)), 2.56–2.50 (m, 1H, –CH_2(C=O)), 2.26–2.20 (m, 1H, –NCH_2CH_2), 1.94–1.86 (m, 1H, –NCH_2CH_2), 1.32–1.24 (m, 3H, –OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 155.6, 154.5, 136.7, 136.5, 128.4, 127.9, 127.8, 127.7, 66.9, 66.8, 60.8, 60.4, 56.1, 50.4, 44.4, 43.6, 37.7, 29.9, 13.9; DEPT (100 MHz, $CDCl_3$) δ 128.4(+), 127.9(+), 127.8(+), 127.7(+), 66.9(−), 66.8(−), 60.8(−), 60.4(+), 56.1(+), 50.4(−), 44.4(−), 43.6(−), 37.7(−), 29.9(−), 13.9(+); HRMS (EI) *m/z* calcd ($C_{24}H_{28}N_2O_6$–H^+): 439.1869, found: 439.1866.

4.9.14. Benzyl-2-allyl-3-[(methoxycarbonyl)amino]-1-pyrrolidinecarboxylate (9d, Table 6, entry 4). Prepared following method H using **5c** (475 mg, 1.54 mmol), allyltrimethylsilane (489 μl, 3.08 mmol, 2 quiv) and $BF_3\cdot OEt_2$ (782 μl, 6.2 mmol, 4 quiv) to yield the substituted pyrrolidine which was purified by flash chromatography (SiO_2, 40%EtOAc/60% hexane) affording a *cis*/*trans*-**9d** mixture (23/77) (385 mg, 79%) as a colorless oil; R_f=(10% EtOAc/90% hexane); IR (film) ν 3316, 3061, 3030, 2951, 1703, 1699, 1694, 1683, 1538, 1455, 1418, 1350, 1280, 1248, 1194, 1114, 918, 770, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.34–7.26 (m, 5H, Ar), 5.82–5.20 (m, 1H, –C*H*=CH_2), 5.16–5.04 (m, 5H, –CH_2Ph and –CH=CH_2 and –N*H*), 4.04 (br, 1H, –C*H*NH(CO_2Me)), 3.79 (br, 1H, –NC*H*CH_2), 3.68 (s, 3H, –OCH_3), 3.64–3.43 (m, 2H, –NC$H_2$$CH_2$), 2.55–2.38 (m, 1H, C$H_2$CH=$CH_2$), 2.21–2.14 (m, 2H, 1×C$H_2$CH=$CH_2$ and 1×–NCH_2CH_2), 2.12–1.83 (m, 1H, –NCH_2CH_2); ^1H NMR (400 MHz, d_2-tetrachloroethane, T=365 K), δ 7.39–7.31 (m, 5H, Ar), 5.81–5.78 (m, 1H, –C*H*=CH_2), 5.19–5.06 (m, 5H, –CH_2Ph and –CH=CH_2 and –N*H*), 4.00 (br, 1H, –C*H*NH(CO_2Me)), 3.79 (d, J=4.8 Hz, 1H, –NC*H*CH_2), 3.64 (s, 3H, –OCH_3), 3.51–3.45 (m, 2H, –NC$H_2$$CH_2$), 2.53 (br, 0.5H, C$H_2$-CH=$CH_2$), 2.42 (br, 0.5H, C$H_2$CH=$CH_2$), 2.19–2.18 (m, 2H, 1×C$H_2$CH=$CH_2$ and 1×–NCH_2CH_2), 1.83 (br, 1H, –NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 156.5, 133.9, 128.7, 128.2, 128.1, 118.3, 67.2, 67.0, 63.9, 55.1, 54.3, 52.3, 44.7, 44.4, 37.9, 37.0, 30.2, 29.2; HRMS (EI) *m/z* calcd for ($C_{17}H_{22}N_2O_4+H^+$): 319.1658, found: 319.1665.

4.9.15. Benzyl-3-azido-2-(2-ethoxy-2-oxoethyl)-1-pyrrolidinecarboxylate (9e, Table 6, entry 5). Prepared following method H using **6a** (237 mg, 0.86 mmol), *tert*-butyl[1-ethoxyvinyl)oxy]dimethylsilane (347 mg, 1.72 mmol) and $BF_3\cdot OEt_2$ (435 μl, 3.4 mmol) to yield the pyrrolidine derivative which was purified by flash chromatography (SiO_2, 20% EtOAc/80% hexane) affording a *cis*/*trans* mixture (88/12) **9e** (140 mg, 49%) as a colorless oil; R_f=0.24 (10% EtOAc/90% hexane); IR (film) ν 2977, 2893, 2099, 1726, 1691, 1448, 1413, 1352, 1261, 1189, 1117, 1029, 899, 766, 694, 598 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.36–7.26 (m, 5H, Ar), 5.12 (br, 2H, –CH_2Ph), 4.34 (br, 2H, –NC*H* and C*H*N_3), 4.19–4.09 (m, 2H, –OC$H_2$$CH_3$), 3.62–3.56 (m, 1H, –NC$H_2$), 3.56–3.39 (m, 1H, –NC$H_2$), 2.66–2.49 (m, 2H, –C$H_2$(C=O)), 2.13–2.19 (m, 2H, –NCH_2CH_2), 1.29–1.25 (m, 3H, CH_2CH_3); ^1H NMR (400 MHz, d_2-tetrachloroethane, T=365 K) δ 7.42–7.34 (m, 5H, Ar), 5.19 (br, 2H, –CH_2Ph), 4.45–4.41 (m, 1H, –NC*H*), 4.32 (q, J=6.4 Hz, 0.88H, –C*H*N_3), 4.21 (dq, J=7.2, 1.6 Hz, 2H, –OC$H_2$$CH_3$), 4.88–4.87 (m, 0.12H, –C*H*N_3), 3.67–3.61 (m, 1H, –NCH_2), 3.58–3.45 (m, 1H, –NCH_2), 2.99 (dd, J=16.4, 4.0 Hz, 0.88H, –CH_2(C=O)),

2.91 (dd, $J=15.6$, 3.6 Hz, 0.12H, $-CH_2(C{=}O)$), 2.70–2.61 (m, 0.88H, $-CH_2(C{=}O)$), 2.48–2.41 (m, 0.12H, $-CH_2(C{=}O)$), 2.22–2.00 (m, 2H, $-NCH_2CH_2$), 1.31 (t, $J=7.2$ Hz, 3H, $-OCH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 170.4, 169.7, 168.3, 157.4, 153.7, 135.6, 127.6, 127.2, 127.1, 66.1, 61.8, 60.0, 59.8, 56.3, 55.4, 44.1, 43.4, 34.2, 33.1, 29.0, 28.1, 13.4; HRMS (EI) m/z calcd for ($C_{16}H_{20}N_4O_4+H^+$): 333.1576, found: 333.1571.

4.9.16. Benzyl-2-allyl-3-azido-1-piperidinecarboxylate (9f, Table 6, entry 6). Prepared following method H using **6b** (70 mg, 0.24 mmol), allyltrimethylsilane (77 µl, 0.48 mmol, 2 quiv) and $BF_3\cdot OEt_2$ (122 µl, 0.96 mmol, 4 quiv) to yield the 3-azido-2-allyl-piperidine which was purified by flash chromatography (SiO_2, 10% EtOAc/90% hexane) affording a *cis*/*trans* mixture (88/12) **9f** (36 mg, 50%) as a colorless oil; $R_f=0.32$ (10% EtOAc/90% hexane); IR (film) ν 2949, 2855, 2100, 1698, 1425, 1347, 1252, 1196, 1146, 1028, 917, 763, 698, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.36–7.26 (m, 5H, Ar), 5.68 (br, 1H, $-CH{=}CH_2$), 5.15–5.03 (m, 4H, $-CH_2Ph$ and $-CH{=}CH_2$), 4.38 (br, 1H, $-NCH$), 4.12 (d, $J=12.8$ Hz, 1H, $-NCH_2$), 3.69 (br, 1H, $-NCHN_3$), 2.86 (dt, $J=12.8$, 4.0 Hz, 1H, $-NCH_2$), 2.47–2.24 (m, 3H, $CH_2CH{=}CH_2$ and 1×$-NCH_2CH_2$), 1.82–1.49 (m, 3H, 1×$-NCH_2CH_2$ and $-NCH_2CH_2CH_2$); ^1H NMR (400 MHz, d_2-tetrachloroethane, $T=365$ K), rotamers, δ 7.40–7.33 (m, 5H, Ar), 5.78–5.72 (m, 1H, $-CH{=}CH_2$), 5.19–5.09 (m, 4H, $-CH_2Ph$ and $-CH{=}CH_2$), 4.43 (t, $J=7.2$ Hz, 0.88H, $-NCH$), 4.30–4.20 (m, 0.12H, $-NCH$), 4.13 (d, $J=11.4$ Hz, 1H, $-NCH_2$), 3.68 (d, $J=1.4$ Hz, 1H, $-NCHN_3$), 2.91 (dt, $J=12.0$, 4.0 Hz, 1H, $-NCH_2$), 2.51–2.41 (m, 1H, $CH_2CH{=}CH_2$), 2.37–2.27 (m, 1H, $CH_2CH{=}CH_2$), 1.83–1.77 (m, 4H, $-NCH_2CH_2$ and $-NCH_2CH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 156.0, 137.0, 133.8, 128.8, 128.6, 128.4, 128.2, 128.1, 128.1, 128.0, 118.2, 70.4, 67.6, 67.4, 58.3, 56.3, 55.6, 54.3, 53.9, 40.4, 38.7, 34.3, 26.05, 23.5, 22.1, 19.8; HRMS (EI) m/z calcd for ($C_{16}H_{20}N_4O_2+H^+$): 301.1664, found: 301.1663.

4.9.17. *trans*-Benzyl-2-allyl-3-iodo-1-pyrrolidinecarboxylate (9g, Table 6, entry 7). Prepared following method H using **2f** (525 mg, 1.45 mmol), allyltrimethylsilane (467 µl, 2.9 mmol, 2 quiv) and $BF_3\cdot OEt_2$ (369 µl, 2.9 mmol, 2 quiv) to yield the substituted pyrrolidine which was purified by flash chromatography (SiO_2, 20%EtOAc/80% hexane) affording **9g** (500 mg, 93%) as a colorless oil; $R_f=0.43$ (20% EtOAc/80% hexane); IR (film) ν 3068, 3033, 2891, 1703, 1641, 1498, 1445, 1411, 1358, 1336, 1287, 1267, 1155, 1110, 916, 875, 768, 735, 697, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) rotamers δ 7.29–7.19 (m, 5H, Ar), 5.70–5.68 (m, 1H, $-CH_2CH{=}CH_2$), 5.16–4.95 (m, 4H, $-CH_2Ph$ and $-CH_2CH{=}CH_2$), 4.20 (br, 2H, CHI and $-NCHCH_2$), 3.72–3.70 (m, 1H, $-NCH_2CH_2$), 3.46–3.43 (m, 1H, $-NCH_2CH_2$), 2.43–2.03 (m, 4H, $-CH_2CH{=}CH_2$ and NCH_2CH_2); ^1H NMR (400 MHz, d_2-tetrachloroethane, $T=360$ K) δ 7.41–7.35 (m, 5H, Ar), 5.83–5.76 (m, 1H, $-CH_2CH{=}CH_2$), 5.22 (s, 2H, $-CH_2Ph$), 5.19–5.10 (m, 2H, $-CH_2CH{=}CH_2$), 4.39–4.26 (m, 2H, $-CHI$ and $-NCHCH_2$), 3.87–3.81 (m, 1H, $-NCH_2CH_2$), 3.54 (dt, $J=8.4$, 2.8 Hz, 1H, $-NCH_2CH_2$), 2.51–2.47 (m, 1H, $-CH_2CH{=}CH_2$), 2.42–2.33 (m, 1H, $-NCH_2CH_2$), 2.26–2.19 (m, 2H, 1×$CH_2CH{=}CH_2$ and 1×NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.6, 136.5, 136.3, 133.6, 133.4, 128.5, 128.0, 127.7, 118.4, 69.0, 68.6, 67.0, 66.9, 45.6, 45.3, 38.8, 38.0, 35.6, 35.8, 25.5, 24.8; DEPT (100 MHz, $CDCl_3$), rotamers, δ 133.6(+), 133.4(+), 128.5(+), 128.0(+), 127.7(+), 118.4(−), 69.0(+), 68.6(+), 67.0(−), 66.9(−), 45.6(−), 45.3(−), 38.8(−), 38.0(−), 35.6(−), 35.8(−), 25.5(+), 24.8(+).

4.9.18. *trans*-Dimethyl-2-{[(benzyloxy)carbonyl]-3-iodo-2-pyrrolidinyl}malonate (9h, Table 6, entry 8). To a stirred solution of **2f** (191 mg, 0.53 mmol) and dimethylmalonate (92 µl, 0.79 mmol, 1.5 quiv) in dry dichloromethane, under argon and cooled to −78 °C was slowly added a solution of $TiCl_4$ (100 µl, 0.53 mmol) in dry dichloromethane. The resulting mixture was stirred at −78 °C for 2 h, warmed to rt and stirred for an additional 2 h. A basic work-up (method F) yielded the substituted pyrrolidine which was purified by preparative thin layer chromatography (40% EtOAc/60% hexane) affording **9h** (165 mg, 68%) as a colorless oil; $R_f=0.35$ (30% EtOAc/70% hexane); IR (film) ν 3037, 2952, 2894, 1735, 1704, 1498, 1435, 1410, 1360, 1335, 1307, 1261, 1198, 1152, 1113, 1028, 974, 753, 698, 665; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.22 (m, 5H, Ar), 5.09–5.06 (m, 2H, $-CH_2Ph$), 4.73 (d, $J=5.5$ Hz, 0.5H, $-CH(CO_2Me)_2$), 4.59 (br, 0.5H, $-CH(CO_2Me)_2$), 3.90–3.31 (m, 10H, $-CHI$, $-NCHCH(CO_2Me)_2$, $-O(CH_3)_2$ and $-NCH_2CH_2$), 2.20–2.14 (m, 2H, NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 167.7, 166.8, 155.4, 137.0, 136.5, 128.8, 128.2, 127.7, 68.6, 68.0, 67.4, 67.1, 54.2, 53.4, 52.7, 52.5, 52.4, 45.9, 45.6, 41.1, 36.3, 35.5, 22.7, 22.0; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.8(+), 128.2(+), 127.7(+), 68.6(+), 68.0(+), 67.4(−), 67.1(−), 54.2(+), 53.4(+), 52.7(+), 52.5(+), 52.4(+), 45.9(−), 45.6(−), 41.1(−), 36.3(−), 35.5(−), 22.7(+), 22.0(+).

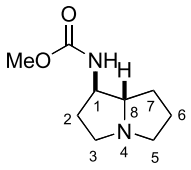
4.10. Synthesis of (±)-laburnamine

4.10.1. *trans*-Benzyl-2-(3-hydroxypropyl)-3-[(methoxycarbonyl)-amino]-1-pyrrolidinecarboxylate (10, Scheme 3). $BH_3\cdot SMe_2$ (30 µl, 0.31 mmol) was added dropwise to a solution of *trans*-**9d** (300 mg, 0.94 mmol) in dry THF (9 ml), cooled in an ice-bath and under nitrogen. The mixture was stirred at rt for 1 h and the solvent removed in vacuo yielding the boronate as a white foam which was dissolved in THF (9 ml). The solution was cooled with an ice-bath and an aqueous 3 M NaOH solution (346 µl, 1.04 mmol) followed by a dropwise addition of an aqueous 30% H_2O_2 solution (343 µl, 3.02 mmol) were added. The mixture was stirred at 40 °C for 2 h and then cold water (10 ml) together with diethyl ether were added (10 ml). The aqueous phase was extracted with diethyl ether, the combined organic layers were dried (Na_2SO_4) and the solvent removed in vacuo. The crude mixture was purified by flash chromatography (SiO_2, 80% EtOAc/20% hexane) affording **10** (170 mg, 55%) as a colorless oil; $R_f=$(10% EtOAc/90% hexane); IR (film) ν 3427, 3313, 3064, 3033, 2951, 1694, 1542, 1498, 1455, 1420, 1351, 1285, 1251, 1116, 1045, 987, 916, 877, 770, 739, 698, 605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.33–7.26 (m, 5H, Ar), 5.30, 5.29 (s, 1H, NH), 5.19–5.01 (m, 2H, $-CH_2Ph$), 3.96 (br, 1H, $-CHNH(CO_2Me)$), 3.80–3.79 (m, 1H,

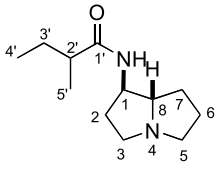
–NC*H*CH_2), 3.62 (s, 3H, CO_2CH_3), 3.67–3.23 (m, 4H, –NCH_2CH_2 and –CH_2CH_2–OH), 2.18–2.15 (m, 1H, –NCH_2CH_2), 1.83–1.77 (m, 1H, –NCH_2CH_2), 1.65–1.24 (m, 4H, –$CH_2CH_2CH_2$–OH); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.8, 155.3, 136.8, 128.7, 128.3, 128.1, 128.0, 67.2, 67.1, 64.4, 64.2, 62.3, 55.6, 55.1, 52.3, 44.5, 44.2, 30.1, 29.8, 29.3, 29.0; HRMS (EI) *m/z* calcd for ($C_{17}H_{24}N_2O_5+H^+$): 337.1763, found: 337.1767.

4.10.2. *trans*-Benzyl-3-[(methoxycarbonyl)amino]-2-(3-{[(4-methylphenyl)sulfonyl]oxy}propyl)-1-pyrrolidinecarboxylate (11, Scheme 3). To a solution of **10** (170 mg, 0.5 mmol) in dry chloroform (0.5 ml) cooled with an ice bath and under argon was added tosyl chloride (194 mg, 1.0 mmol) and right after, pyridine (82 μl, 1.0 mmol). The reaction mixture was stirred for 3 h at rt and water (2 ml) was then added followed by diethyl ether (5 ml). The organic phase was washed with an HCl (2 M, 3 ml), 5% $NaHCO_3$ aqueous solution (3 ml), water (3 ml) and dried with anhydrous $MgSO_4$. The reaction mixture was stirred for 3 h at rt. The solvent was removed in vacuo and the residue purified by preparative thin layer chromatography (60% EtOAc/40% hexane) to yield **11** (60 mg, 68%) as a colorless oil; R_f=0.64 (80% EtOAc/20% hexane); IR (film) ν 3319, 2956, 1704, 1532, 1435, 1359, 1175, 1097, 925, 664 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.73–7.67 (m, 2H, Ar), 7.29–7.20 (m, 7H, Ar), 5.11–4.83 (m, 2H, CH_2Ph), 4.83 (br, 1H, N*H*), 4.02–3.93 (m, 1H, –CH_2OTs), 3.89 (br, 1H, –*C*HNH(CO_2Me)), 3.82 (br, 1H, –NC*H*CH_2), 3.57 (s, 3H, –OCH_3), 3.66–3.36 (m, 2H, –CH_2OTs and –NCH_2CH_2), 2.38 (s, 3H, Ar-CH_3), 2.25–2.06 (m, 1H, –NCH_2CH_2), 1.79–1.19 (m, 5H, 1×–NCH_2CH_2 and –$CH_2CH_2CH_2$OTs); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 156.2, 154.9, 144.7, 136.6, 133.0, 129.8, 129.5, 128.8, 128.5, 128.0, 127.8, 126.0, 125.7, 70.5, 70.3, 70.02, 67.05, 66.9, 63.7, 55.4, 54.7, 52.1, 44.2, 43.9, 29.8, 29.6, 29.3, 28.8, 25.6, 21.6; HRMS (EI) *m/z* calcd for ($C_{24}H_{30}N_2O_7S+H^+$): 491.1851, found: 491.1844.

4.10.3. *trans*-Methyl-hexahydro-1*H*-pyrrolizin-1-ylcarbamate (12, Scheme 3). To a solution of **11** (96 mg, 0.196 mmol) in dry ethanol (0.2 ml), cooled in an ice bath and under argon, was added palladium over carbon (19 mg). The reaction mixture was placed in a hydrogen atmosphere and stirred vigorously overnight. The solvent was removed and a KOH 2 M aqueous NaCl saturated solution (5 ml) was added to the residue and extracted with diethyl ether (4× 5 ml). The combined organic layers were dried under Na_2SO_4 and the solvent removed in vacuo. The residue was purified by preparative thin layer chromatography (MeOH/CH_2Cl_2/NH_4OH, 10:89:1) to yield **12** (20 mg, 56%) as an orange oil; R_f=0.2 (CH_2Cl_2/MeOH/NH_4OH: 8/2/0.1, I_2); IR (film) ν 3451, 2951, 2514, 1711, 1536, 1452, 1254, 1193, 909, 780, 666 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.2–4.15 (m, 2H, H_1 and H_8), 3.93–3.68 (m, 1H, H_3), 3.9–3.63 (m, 1H, H_5), 3.6 (s, 3H, –OCH_3), 2.98–2.87 (m, 2H, H_3 and H_5), 2.32–2.18 (m, 2×H_2 and 1×H_7), 2.05–1.97 (m, 1×H_6 and 1×H_7), 1.84–1.76 (m, 1×H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 71.5, 55.9, 55.2, 53.2, 52.4, 31.7, 31.1, 30.0, 25.4; HRMS (EI) *m/z* calcd for ($C_9H_{16}N_2O_2+H^+$): 185.1290, found: 185.1280.



4.10.4. *trans*-*N*-Hexahydro-1*H*-pyrrolizin-1-yl-2-methylbutanamide((±)-laburnamine) (13, Scheme 3). To a solution of **12** (50 mg, 0.27 mmol) in dry chloroform (0.27 ml) under argon was added iodo(trimethyl)silane (47 μl, 0.32 mmol). The mixture was heated to 60 °C and stirred for 4 h. Methanol (0.1 ml) was then added and the volatile components removed in vacuo. The residue was redissolved in methanol and sodium methoxide was added (8 mg, 0.14 mmol). The mixture was stirred for 10 min at 60 °C and the volatile components removed in vacuo, to yield the crude amine, which was immediately used in the next reaction. To a solution of crude amine (50 mg, 0.27 mmol) in THF (2,7 ml), cooled in an ice bath and under argon, was added triethylamine (56 μl, 0.4 mmol) followed by (±)-2-methylbutyric acyl chloride (40 μl, 0.32 mmol). The reaction mixture was stirred for 4 h at rt and the solvent removed in vacuo. The residue was dissolved in methanol (5 ml) and a KOH pellet was added. After stirring for 10 min the solvent was removed in vacuo and the crude reaction mixture was purified by preparative thin layer chromatography (MeOH/CH_2Cl_2/NH_4OH, 10:89:1), to yield the (±)-laburnamine **13** (36.4 mg, 64%) as an orange oil; R_f=0.3 (CH_2Cl_2/MeOH/NH_4OH: 8/2/0.1, I_2); IR (film) ν 3437, 3270, 2965, 2934, 1704, 1645, 1548, 1463, 1386, 1289, 1238, 1089, 1013 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (br, 1H, NH), 3.71–3.65 (m, 1H, H_1), 3.58–3.43 (m, 1H, H_8), 3.39–3.19 (m, 1H, H_3), 2.81–2.67 (m, 2H, H_3, H_5), 2.21–2.14 (m, 3H, 2×H_2, H_5), 2.01–1.81 (m, 4H, 2×H_6, H_7, $H_{2'}$), 1.75–1.57 (m, 2H, H_7, $H_{3'}$), 1.46–1.36 (m, 1H, $H_{3'}$), 1.11–1.09 (m, 3H, 3×$H_{5'}$), 0.89–0.71 (m, 3H, 3×$H_{4'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.2, 55.0, 53.8, 53.0, 42.6, 31.7, 30.1, 27.2, 25.3, 17.3, 11.8; DEPT (100 MHz, $CDCl_3$) δ 71.2(+), 55.0(−), 53.8(+), 53.0(−), 42.6(+), 31.7(−), 30.1(−), 27.2(−), 25.3(−), 17.3(+), 11.8(+); HRMS (EI) *m/z* calcd for ($C_{12}H_{22}N_2O+H^+$): 211.1810, found: 211.1812.



Acknowledgements

This work was supported by the Fundação para a Ciência e Tecnologia and FEDER (Ref. PRAXIS XXI PCEX/QUI/53/96 and PRAXIS XXIBD/9040/96) and the National Science and Engineering Research Council (NSERC) of Canada. We thank Mr. Paul Lee and Mr. Timothy McGarvey for running some preliminary experiments. We thank Dr. A. B. Young for mass spectroscopic analysis and Dr. A. J. Lough for X-ray crystal structure determination.

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